38 Cancer of the Head and Neck

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INCIDENCE AND ETIOLOGY

The estimated number of new head and neck cancer cases (excluding skin cancer) in the United States in 2013 is 53,640; this represents 3.2% of the total new cancer cases.[1] Approximately 27% of these patients are women.[1] African Americans have a higher age-adjusted incidence than other ethnic groups. The usual time of diagnosis is after the age of 40, except for salivary gland and nasopharyngeal cancers (NPCs), which may occur in younger age groups. For many primary sites, tobacco use is associated with an increased risk. Alcohol has also been implicated as a causative factor; the effects of alcohol and tobacco may be synergistic.[2] Head and neck cancer patients have an increased risk for developing a second primary tumor (SPT), both within the head and neck and elsewhere (e.g., esophageal and lung cancers),[3] attributed to the field effect associated with tobacco and alcohol use.[4] Human papillomavirus infection (HPV; most commonly HPV-16) plays a role in the development of certain head and neck cancers, particularly those in the oropharynx.[5,6] Patients with high-risk HPV (HR-HPV)–positive head and neck cancers tend to be younger and less likely to have a strong history of tobacco and ethanol use, have a history of multiple sex partners (particularly oral-genital sex), have a better prognosis, and appear to have a lower rate of SPTs.[6–8] Prior tobacco exposure adversely affects the prognosis of HPV-related oropharynx cancers.[8,9] An increasing incidence of oral tongue squamous cell carcinoma in nonsmoking Caucasian women has been reported that does not appear to be driven by prior HPV infection, whereas the incidence of other oral cavity cancers is declining.[10] There is a long-standing association between Epstein-Barr virus (EBV) and NPC.[11] Occupational exposures are associated with the development of sinonasal tract tumors.[12]

ANATOMY AND PATHOLOGY

The anatomy pertaining to a particular primary site is described in subsequent sections. To facilitate communication, lymph nodes are organized into levels. Level I includes the submental and submandibular areas; levels II through IV include the internal jugular vein lymph nodes; level V includes the posterior triangle (Fig. 38.1).[13] Furthermore, which lymph node levels are involved is predictive of the primary site. For example, lip, oral cavity, and facial skin tumors typically spread to levels I and II initially; larynx and pharynx cancers have a predilection for spread to levels II and III.

There are no capillary lymphatics in the epithelium. The tumor must penetrate the lamina propria before lymphatic invasion can occur. One can predict the richness of the capillary network in a given head and neck site by the relative incidence of lymph node metastases at presentation. The nasopharynx and pyriform sinus have the most profuse capillary lymphatic networks. The paranasal sinuses, middle ear, and vocal cords have few or no capillary lymphatics. Muscle and fat contain few capillary lymphatics, as do bone and cartilage within the periosteum or perichondrium. There are no capillary lymphatics in the eye, and few in the orbit.

Most head and neck malignant neoplasms arise from the surface epithelium and are squamous cell carcinoma (SCC) or one of its variants, including lymphoepithelioma, spindle cell carcinoma, verrucous carcinoma, and undifferentiated carcinoma. Lymphomas and a wide variety of other malignant and benign neoplasms make up the remaining cases.[14–16]

Lymphoepithelioma is an SCC with a lymphoid stroma and occurs in the nasopharynx, tonsillar fossa, and base of tongue; it may also occur in the salivary glands. In the spindle cell variant, there is a spindle cell component that resembles sarcoma intermixed with SCC. It is generally managed like other high-grade SCCs. Verrucous carcinoma is a low-grade SCC found most often in the oral cavity, particularly on the gingiva and buccal mucosa. It usually has an indolent growth pattern and is often associated with the chronic use of snuff or chewing tobacco.

Small cell neuroendocrine carcinoma occurs rarely throughout the head and neck. Upper aerodigestive tract lymphomas almost always show a diffuse non-Hodgkin histologic pattern.

NATURAL HISTORY

Patterns of Spread

Primary Lesion

SCCs usually begin as surface lesions. Superficial tumors arising in the Waldeyer ring may be difficult to distinguish from normal lymphoid tissue. Very early surface lesions may show only erythema and a slightly elevated mucosa.

Spread is dictated by local anatomy, and thus varies by each site. Muscle invasion is common, and the tumor may spread along muscle or fascial planes a surprising distance from the palpable or visible lesion. The tumor may attach early to the periosteum or perichondrium, but bone or cartilage invasion is usually a late event. Bone and cartilage usually act as a barrier to spread; the tumor that encounters these structures will often be diverted and spread along a path of less resistance. Slow-growing gingival neoplasms may produce a smooth pressure defect of the underlying bone without bone invasion.

Tumor extension into the parapharyngeal space allows superior or inferior spread from the skull base to the low neck.

Spread inside the lumen of the sublingual, submandibular, and parotid gland ducts is uncommon. The nasolacrimal duct, however, is often invaded in ethmoid sinus and nasal carcinomas.

Perineural invasion (PNI) is observed in SCCs as well as salivary gland tumors, especially adenoid cystic carcinomas. When advanced, PNI may produce neurologic symptoms and is associated with a poorer rate of local control.[17] Tumors may track along a nerve to the skull base and central nervous system (CNS) or peripherally.

Vascular space invasion is associated with an increased risk for regional and distant metastases.

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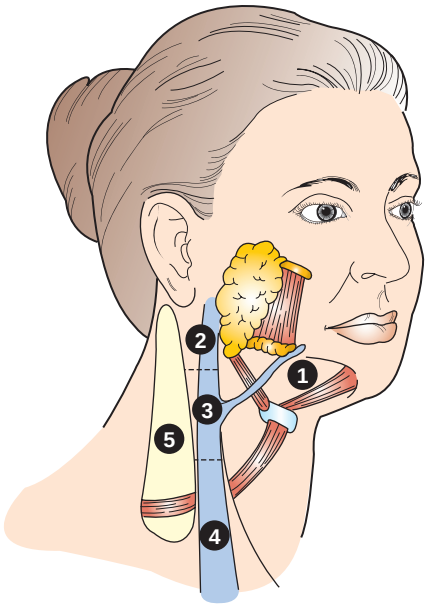

Figure 38.1 Head and neck lymph node levels.

Lymphatic Spread

The differentiation of the tumor, the size of the primary lesion, the presence of vascular space invasion, and the density of capillary lymphatics predict the risk of lymph node metastasis. Recurrent lesions have an increased risk. Histology also impacts the likelihood of lymphatic spread. Low-grade minor salivary gland tumors and sarcomas have a lower risk of lymph node metastases than SCCs arising in similar mucosal sites.

A patient may present with SCC in a cervical lymph node, and despite an extensive work-up, the site of origin may remain undetermined in approximately 50% of patients.[18] If only the neck is treated, a primary lesion may appear later, but sometimes is never found.[19]

The relative incidence of clinically positive lymph nodes on admission is determined by primary site and T stage.[20] Well-lateralized lesions spread to ipsilateral neck nodes.[21] Lesions on or near the midline, tongue base, and nasopharyngeal lesions (even when lateralized), may spread to both sides of the neck, although the risk is higher to the side occupied by the bulk of the lesion. Patients with clinically positive ipsilateral neck nodes are at risk for contralateral disease, especially if the nodes are large or multiple; obstruction of the lymphatic pathways by surgery or radiotherapy (RT) also shunts the lymphatic flow to the opposite neck.[21] When lymph node metastases appear at an unusual site, a careful search must be made for a second primary. The likelihood of retropharyngeal adenopathy is related to the presence of clinically involved lymph nodes and the primary site, and is particularly high for NPCs.[22]

Distant Spread

The risk of distant metastasis is related more to N stage and the location of involved nodes in the low neck, rather than to T stage.[23] The risk is less than 10% for N0 or N1 disease and rises to approximately 30% for N3 disease as well as N1 or N2 nodes with disease below the level of the thyroid notch. Distant metastases are found most often in the lung.[24]

DIAGNOSIS

A general medical evaluation is performed, including a thorough head and neck examination. The location and extent of the primary tumor and any clinically positive lymph nodes is documented. Almost all patients undergo contrast enhanced computed tomography (CT) and/or magnetic resonance imaging (MRI) to further define the extent of local–regional disease. The scan(s) should be obtained prior to biopsy so that biopsy changes are not confused with the tumor. A chest radiograph is obtained to determine the presence of distant metastases and/or a synchronous primary lung cancer. Patients with N3 neck disease, as well as those with N2 disease with nodes below the level of the thyroid notch, have a 20% to 30% risk of developing distant metastases and are considered for a chest CT or positron emission tomography (PET).

Tumors amenable to transoral biopsy may be biopsied using local anesthetics in the clinic. Otherwise, direct laryngoscopy under anesthesia is performed to determine the extent of the tumor and to obtain a tissue diagnosis. Given the risk of synchronous cancers, some advocate routine triple endoscopy (i.e., laryngoscopy/pharyngoscopy, bronchoscopy, and esophagoscopy). The additional yield is low, unless diffuse mucosal abnormalities or a malignant lymph node without an identified primary site, particularly in the low neck, are present. Patients presenting with a metastatic node from an unknown primary site undergo fine-needle aspiration (FNA) of the node. An excisional biopsy is not routinely performed unless lymphoma is suspected or FNA results are equivocal. If SCC is a consideration, the excision should be done in a manner to facilitate subsequent management, including neck dissection. Occasionally, the diagnosis may be made by clinical and radiographic evaluation, and a biopsy should be avoided in situations where the treatment is definitive for RT and where obtaining a tissue sample is risky (e.g., paragangliomas, juvenile nasopharyngeal angiofibromas).[14,25]

Before the initial treatment, the patient should be evaluated by members of the team who may be involved in the initial management as well as possible salvage therapy. Head and neck surgeons, radiation oncologists, medical oncologists, diagnostic radiologists, plastic surgeons, pathologists, dentists, speech and swallowing therapists, and social workers may all play a role.

STAGING

The staging system of the American Joint Committee on Cancer (AJCC) is used.[26] In general, excisional biopsy (TX) indicates that the primary tumor cannot be assessed; T0 indicates no evidence of primary tumor; and Tis indicates carcinoma in situ. For tumors of the oral cavity and oropharynx, further staging of the primary lesion is based primarily on size criteria: 2 cm or less for T1; greater than 2 cm but no more than 4 cm for T2; greater than 4 cm for T3; and T4 tumors involve major invasion or encasement of surrounding structures (e.g., bone, carotid artery, deep musculature). For the other primary sites, further staging is less easily generalized because the anatomic extent of spread and/or functional criteria (e.g., vocal cord mobility) are used and, for certain sites, are combined with tumor size (e.g., hypopharynx, major salivary glands), and so will be given in the discussion of each respective primary site.[26] Neck staging is common to all head and neck sites, except the nasopharynx (Table 38.1).[26] Lesions may be clinically or pathologically staged. Clinical staging is more commonly used for treatment planning and the reporting of results. The format for combining T and N stages into an overall stage is depicted in Table 38.2 and is common to all sites except the nasopharynx.[26]

Stage IV represents a wide spectrum of disease. One patient may have a T1, T2, or T3 lesion with low-volume N2 neck disease and a high probability of cure (stage IVA), whereas another may have a T4b primary cancer and/or N3 neck disease and a relatively poor prognosis (stage IVB)[27]; distant metastases indicate stage IVC disease, and the treatment intent is typically palliative.

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TABLE 38.1

2010 American Joint Committee on Cancer Stages of Regional Lymph Node Involvement

NX	Regional lymph nodes cannot be assessed
N0	No regional lymph node metastasis
N1	Metastasis in a single ipsilateral lymph node, 3 cm or less in greatest dimension
N2	Metastasis in single ipsilateral lymph node, more than 3 cm but no more than 6 cm in greatest dimension; or in multiple ipsilateral lymph nodes, none more than 6 cm in greatest dimension; or in bilateral or contralateral lymph nodes, no more than 6 cm in greatest dimension
N2a	Metastasis in single ipsilateral lymph node, more than 3 cm but no more than 6 cm in greatest dimension
N2b	Metastasis in multiple ipsilateral lymph nodes, none more than 6 cm in greatest dimension
N2c	Metastasis in bilateral or contralateral lymph nodes, none more than 6 cm in greatest dimension
N3	Metastasis in a lymph node more than 6 cm in greatest dimension

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PRINCIPLES OF TREATMENT FOR SQUAMOUS CELL CARCINOMA

General Principles for Selection of Treatment

Surgery and RT are the only curative treatments for head and neck carcinomas. Although chemotherapy alone is not curative, it enhances the effects of RT, and thus is routinely used as part of combined modality treatment in patients with stage III or IV disease.

The advantages of surgery compared with RT, assuming similar cure rates, may include the following: (1) a limited amount of tissue is exposed to treatment, (2) the treatment time is shorter, (3) the risk of immediate and late RT sequelae is avoided, and (4) RT is reserved for a head and neck SPT, which may not be as suitable for surgery.

TABLE 38.2

2010 American Joint Committee on Cancer Overall Stage Grouping

Stage 0	Tis	N0	M0
Stage I	T1	N0	M0
Stage II	T2	N0	M0
Stage III	T3	N0	M0
	T1–T3	N1	M0
Stage IVA	T4a	N0–N1	M0
	T1–T4a	N2	M0
Stage IVB	Any T	N3	M0
	T4b	Any N	M0
Stage IVC	Any T	Any N	M1

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The advantages of RT may include (1) the risk of a major postoperative complication is avoided, (2) no tissues are removed so that the probability of a functional or cosmetic defect may be reduced, (3) elective neck RT can be included with little added morbidity, and (4) the surgical salvage of RT failure is probably more likely than the salvage of a surgical failure.

Salvage of a surgical failure may be attempted by operation, RT, or both. Surgical recurrences usually develop at the resection margins, in or near the suture line. It is difficult to distinguish the normal surgical scarring from recurrent disease, and the diagnosis of recurrence is often delayed. Tumor response to RT under these circumstances is poor. Surgery, RT, or both, however, may salvage small mucosal recurrences and some neck recurrences. For bulkier recurrences treated with RT, concurrent chemotherapy is often incorporated.

MANAGEMENT

Primary Site

The management of the primary cancer will be considered separately for each anatomical site. Patients who are in poor nutritional condition may require a nasogastric (NG) tube or a percutaneous gastrostomy (PEG) before initiating RT, particularly if concomitant chemotherapy is used. Opinions vary regarding the role of prophylactic NG or PEG placement in anticipation of RT-based local toxicity in patients without significant baseline dysphagia or weight loss; a reactive strategy is preferred by many and may facilitate swallowing recovery.[28] If external-beam radiotherapy (EBRT) is selected, it may be given with either conventional once-daily fractionation, 66 to 70 Gy at 2 Gy per fraction, 5 days a week in a continuous course, or with an altered fractionation schedule. Whether an altered fractionation schedule is better than conventional fractionation depends on the altered fractionation technique that is selected. Two altered fractionation schedules shown to result in improved local–regional control rates are the University of Florida hyperfractionation and the M.D. Anderson concomitant boost techniques.[29] The results of a prospective randomized Radiation Therapy Oncology Group (RTOG) trial comparing these schedules with conventional fractionation and the Massachusetts General Hospital accelerated split-course schedule are shown in Table 38.3. Acute toxicity is increased with altered fractionation; late toxicity is comparable with conventional fractionation.[30]

Conventional EBRT techniques and/or brachytherapy will be discussed in the subsequent site-specific sections. EBRT may also be delivered with intensity-modulated radiation therapy (IMRT) to produce a more conformal dose distribution and to reduce the dose to the normal tissues.[31–33] The disadvantages of IMRT are that it is more time consuming to plan and treat the patient, the dose distribution is often less homogenous so that "hot spots" may increase the risk of late complications, the risk of a marginal miss may be increased because the fields are more conformal, the total body RT dose is higher because of increased "beam on" time and scatter irradiation, and it is more costly. Therefore, a clear reason for using IMRT versus conventional RT must be identified. The usual indication for IMRT is to reduce the dose to the contralateral parotid gland, and thus limit long-term xerostomia.[34] Another indication is to reduce the CNS dose in patients with NPC. Finally, it may be used to avoid a difficult low neck match in patients with laryngeal or hypopharyngeal cancers and a low-lying larynx. Proton therapy, which offers potential targeting and dosing advantages for selected tumors,[35] is useful for reducing the dose to the brain and the visual apparatus for patients with nasal cavity and paranasal sinus malignancies.

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TABLE 38.3

Altered Fractionation: 5-Year Outcomes from the Radiation Therapy Oncology Group 90-03 Trial

Parameter	Fractionation Schedule			
	Conventional (70 Gy/35 Fx/7 wk)	Hyperfractionation (81.6 Gy/68 Fx/7 wk)	Accelerated Split Course (67.2 Gy/42 Fx/6 wk)	Accelerated Concomitant Boost (72 Gy/42 Fx/6 wk)
Number of patients	268	263	274	268
Local–regional failure	59.1%	51.2% (p = 0.037)	57.8% (p = 0.042)	51.7%
Disease-free survival	21.2%	30.7% (p = 0.013)	26.6% (p = 0.042)	28.9%
Overall survival	29.5%	37.1% (p = 0.063)	30.8%	33.5%
Cause-specific survival	42.9%	45.5%	40.9%	43.4%
Grade 3 late toxicity	25.2%	27.4%	26.8%	33.3% (p = 0.066)

Note: P values reflect comparison of the experimental arms with standard fractionation.
Fx, fractions.
From Trotti A, Fu KK, Pajak TF, et al. Long term outcomes of RTOG 90-03: a comparison of hyperfractionation and two variants of accelerated fractionation to standard fractionation radiotherapy for head and neck squamous cell carcinoma. *Int J Radiat Oncol Biol Phys* 2005;63:S70–S71.

NECK

In a classic *radical neck dissection*, the superficial and deep cervical fascia with its enclosed lymph nodes (levels I to V) is removed in continuity with the sternocleidomastoid muscle, the omohyoid muscle, the internal and external jugular veins, cranial nerve XI, and the submandibular gland. The incisions used by the surgeon will be governed largely by the primary lesion. The radical neck dissection can be *modified* to spare certain structures with the intent of decreasing morbidity and improving functional outcome without compromising disease control. There are three main types of modified radical neck dissections: type I, CN XI is spared; type II, CN XI and the internal jugular vein are spared; and type III (functional), CN XI, the internal jugular vein, and the sternocleidomastoid muscle are spared. *Selective* neck dissections are more limited and include the resection of lymph node levels that are at greatest risk for nodal metastatic spread. Examples include the lateral, posterolateral, and supraomohyoid, which include resections of lymph node levels II through IV, II through V, and I through III, respectively.

A modified or selective neck dissection is recommended for the cN0 neck, for selected clinically positive necks (mobile, 1 to 3 cm lymph nodes), and for removing residual disease after RT when there has been excellent regression of N2 or N3 disease.[36,37]

The more extensive the neck dissection, the higher the risk of complications. Complications after neck dissection include hematoma, seroma, lymphedema, wound infections and dehiscence, damage to the 7th, 10th, 11th, and 12th cranial nerves, carotid exposure, and carotid rupture. The last-mentioned complication can be minimized by covering the carotid artery with a dermal graft at the time of surgery.[36] Pain and dysfunction in the neck or shoulder may occur. Rehabilitation and anti-inflammatory medication are commonly utilized with varying benefits; acupuncture had demonstrated a benefit compared to the usual care in one randomized study.[38]

Clinically Negative Neck

The estimated incidence of subclinical disease in the regional lymphatics when the neck is cN0 is presented in Table 38.4.[39] Both RT and neck dissection are approximately 90% efficient at eradicating subclinical regional disease.[36] Alternatively, a policy of close observation may be adopted for the cN0 neck to avoid unnecessary treatment, and the neck is managed by surgery and/or RT if cervical metastases develop. The salvage rate for patients developing clinically positive lymph nodes with the primary lesion controlled is 50% to 60%.[39]

TABLE 38.4

Definition of Risk Groups for the Clinically N0 Neck

Group	Estimated Risk of Subclinical Neck Disease	T Stage	Site
I: Low risk	<20%	T1	Floor of mouth, oral tongue, retromolar trigone, gingiva, hard palate, buccal mucosa
II: Intermediate risk	20%–30%	T1 T2	Soft palate, pharyngeal wall, supraglottic larynx, tonsil Floor of mouth, oral tongue, retromolar trigone, gingiva, hard palate, buccal mucosa
III: High risk	>30%	T1–T4 T2–T4 T3–T4	Nasopharynx, pyriform sinus, base of tongue Soft palate, pharyngeal wall, supraglottic larynx, tonsil Floor of mouth, oral tongue, retromolar trigone, gingiva, hard palate, buccal mucosa

Reprinted with permission from Mendenhall WM, Million RR. Elective neck irradiation for squamous cell carcinoma of the head and neck: analysis of time-dose factors and causes of failure. *Int J Radiat Oncol Biol Phys* 1986;12:741–746.

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TABLE 38.5

Failure of Initial Neck Treatment (596 Patients with Carcinoma of the Tonsillar Fossa, Base of Tongue, Supraglottic Larynx, or Hypopharynx at M.D. Anderson Hospital 1948–1967)

	Stage							
	N0							
Treatment	No Treatment	Partial	Complete	N1	N2A	N2B	N3A	N3B
Radiation		15%	2%	15%	27%	27%	38%	34%
Surgery	55% (16/29)	35%	7%	11%	8%	23%	42%	41%
Combined		1/5	0/6	0	0	0	23%	25%

Adapted from Barkley HT Jr, Fletcher GH, Jesse RH, et al. Management of cervical lymph node metastases in squamous cell carcinoma of the tonsillar fossa, base of tongue supraglottic larynx, and hypopharynx. *Am J Surg* 1972;124:462–467.

Elective neck irradiation (ENI) and elective neck dissection are equally effective in the management of the N0 neck, with control rates exceeding 90%.[39,40] Treatment of the entire neck is advised for primary lesions with a high rate of subclinical disease, such as the base of tongue, soft palate, supraglottis, and hypopharynx. Patients with lateralized T1 to T2 tonsillar cancers do not require elective treatment for the contralateral N0 neck[41]; T3 or T4 cancers or those with significant extension into the tongue and/or soft palate should receive bilateral neck treatment to the entire neck.

When the primary tumor is to be treated surgically, an elective neck dissection should be performed when the risk of regional lymph node metastasis is 10% to 15% or greater. Modified neck dissection has a good rate of disease control; patients who are found to have multiple positive nodes or extracapsular extension (ECE) are then referred for postoperative RT,[42] and concurrent chemotherapy is recommended in the latter circumstance.[43–46] If the primary lesion is to be treated with EBRT, ENI adds relatively little cost and modest morbidity.

Clinically Positive Neck Lymph Nodes

The rates of neck failure by N stage and treatment group reported from the M.D. Anderson Cancer Center and the University of Florida are shown in Tables 38.5 and 38.6, respectively.[40,47] In general, RT precedes surgery if the primary site is to be treated by RT or if the node was fixed. The operation precedes RT if the primary site is to be treated surgically.

Modified neck dissection is sufficient treatment for the ipsilateral neck for patients with N1 or N2A disease without ECE. RT, often combined with concurrent chemotherapy, is added for those with more advanced neck disease.[42]

When the primary lesion is to be managed by RT or chemoradiotherapy (chemoRT), then RT-based therapy alone is sufficient for patients in whom the node(s) regress completely as documented on CT obtained 4 weeks post-RT.[37,48] RT is followed by a neck dissection for patients with residual nodes that are 1.5 cm or larger, as well as those that demonstrate focal defects, enhancement, and/or calcification.[48] A PET scan done 3 months after RT is completed is an alternative to CT to assess whether there is persistent disease.[49]

McGuirt and McCabe[50] compared results of definitive surgery with and without a prior open neck biopsy and concluded the risks of neck failure, distant metastases, and complications were all increased. Ellis et al.[51] studied the results of therapy following open biopsy of a lymph node before treatment. Patients received definitive RT to the primary site and neck; a subset of patients underwent a neck dissection after RT. Open biopsy had no adverse impact on these patients compared with those who did not undergo an open biopsy.[51] Therefore, after open biopsy of the neck, RT-based therapy is recommended as the initial treatment, particularly if the primary tumor is to be managed by RT or chemoRT. Under these circumstances, no further neck treatment is needed if the neck node had been removed; if there was residual gross tumor in the neck after open biopsy, a planned neck dissection should be added depending on the results of radiologic reassessment.[48]

TABLE 38.6

5-Year Rate of Neck Control According to the 1983 American Joint Committee on Cancer Stage and Treatment (459 Patients, 593 Hemincks[a])

	RT Alone		RT + Neck Dissection		
Stage	No. of Heminecks	Control	No. of Heminecks	Control	Significance
N1	215	86%	38	93%	$p = 0.28$
N2A	29	79%	24	68%	$p = 0.60$
N2B	138	70%	80	91%	$p < 0.01$
N3A	29	33%	40	69%	$p < 0.01$

Note: The University of Florida data, patients were treated October 1964 to October 1985; analysis occurred December 1988 by Eric R. Ellis, MD.
[a] Excludes 67 heminecks that received incisional or excisional biopsies before treatment.
From Mendenhall WM, Parson JT, Mancuso AA, et al. Head and neck: management of the neck. In: Perez CA, Brady LW, eds. *Principles and Practice of Radiation Oncology*, 2nd ed. Philadelphia: J.B. Lippincott Company; 1992: 790–805; and American Joint Committee on Cancer. *Manual for Staging of Cancer*. Philadelphia: J. B. Lippincott Company; 1983.

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CHEMOTHERAPY

Drug therapy may be administered to prevent the development of SPTs (chemoprevention), to palliate symptoms in patients with incurable disease, to improve the odds of cure or organ preservation when combined with definitive local-regional therapy, or to decrease treatment toxicity. The first two indications are discussed here; the last two are discussed in a subsequent section.

Chemoprevention

Chemoprevention is the administration of natural or synthetic agents to reduce the risk of developing SPTs. Patients who have a head and neck SCC have an increased risk of developing an upper aerodigestive tract SPT because of exposure to carcinogens and/or genetic predisposition.[3] The risk of developing an SPT is approximately 2.7% to 4% per year[52] and may impact survival. Current data indicate the risk of SPTs is lower among patients with HR-HPV–related head and neck cancers.[6,8] Analogs of vitamin A, particularly of the retinoids, have been a particular focus of clinical investigations. At present, there is no standard role for the use of chemopreventive agents in the management of head and neck cancer.

Retinoids and beta-carotene both may cause regression of oral leukoplakia; the former appear more efficacious.[53] Lesions commonly recur after cessation of drug therapy. Chemoprevention agents do not reduce the risk of recurrence of the index cancer.

High-dose13-*cis*-retinoic acid (100 mg/m^2 daily for 12 months) has been shown in a randomized, placebo-controlled trial to reduce the risk of SPTs in patients previously treated for stage I to IV, M0, head and neck cancer.[54] However, a large, placebo-controlled, randomized trial in 1,190 survivors of stage I and II head and neck SCC found no difference in the rate of SPTs or survival after 3 years of a low-dose schedule of this agent (30 mg per day).[55] Outcomes were better among nonsmokers and those who quit compared to smokers, emphasizing the important role of tobacco cessation as part of head and neck cancer management and strategies to decrease SPTs. Similarly, etretinate was not shown to be efficacious in decreasing SPTs.[56]

With regard to other agents, vitamin A, N-acetylcysteine, both, or neither were evaluated using a factorial design in the EUROSCAN study. No significant improvement in survival or SPTs was observed.[57] Bairati et al.[58] randomized head and neck cancer survivors to 3 years of therapy with alpha-tocopherol and beta-carotene versus placebo; the rate of SPTs was actually higher during the period of treatment, a difference that did not persist with longer follow-up. A randomized phase II, placebo-controlled trial demonstrated no significant benefit of celecoxib at 100 mg or 200 mg, both twice daily, on the control of oral premalignant lesions.[59]

Targeting the epidermal growth factor receptor (EGFR) pathway is receiving attention, because there is an association between progressive EGFR dysregulation and the transition from normal mucosa to dysplasia to SCC.[60] The concept of bioadjuvant therapy,[55] whereby drug combinations intended to reduce both the risk of SPTs and relapse from the index cancer, as well as the potential role of natural extracts are also of interest.[61]

There is no standard role for the use of HR-HPV vaccination in the prevention of head and neck cancer at this time,[62] although the impact of current vaccination programs on the incidence of head and neck cancer warrants follow-up.

Chemotherapy for Recurrent or Metastatic Disease

Single Agents

Patients with recurrent or metastatic head and neck SCCs have a median survival of 6 to 9 months, and a 1-year survival rate of 20% to 40% when treated with chemotherapy alone.[63,64] Although selected patients may derive apparent significant prolongations in survival, average survival improvements appear small at best. Morton et al.[65] reported a 2-month improvement in median survival after treatment with cisplatin, with or without bleomycin, compared to no treatment. The duration of responses is typically measured in weeks to months, not years; survival beyond 2 years is infrequent; and cures are anecdotal. Thus, the primary intent of chemotherapy in this setting is to achieve tumor regression with the hope that the potential palliative benefit and possible modest survival improvement will outweigh the side effects of treatment.

A number of drugs have been demonstrated in clinical trials to have activity in head and neck SCCs, and the list is well summarized in prior reviews.[63,64] The most commonly used include methotrexate, cisplatin, carboplatin, 5-fluorouracil, paclitaxel, and docetaxel, with reported major response rates ranging from 15% to 42%. Among other drugs with reported major response rates of 15% or greater are bleomycin, cyclophosphamide, doxorubicin, hydroxyurea, ifosfamide, irinotecan, oral uracil, ftorafur (with leucovorin), pemetrexed, vinblastine, and vinorelbine. Some of these agents (e.g., cyclophosphamide, doxorubicin, hydroxyurea) have their activity based on reported assessments in a limited number of patients from over 2 decades ago, an era when methods and criteria for response assessments may have differed from current standards. Anticipated response rates and toxicity profiles may vary based on patient selection and drug schedule. A poor performance status is associated with both lower response rates and greater potential for toxicity. The larger the amount of prior treatment also adversely affects response rates.[64]

Methotrexate is a historic standard drug used in the recurrent or metastatic disease setting. The typical standard dosing is 40 mg/m^2 intravenously weekly, with dose attenuation or increase (up to 60 mg/m^2) based on toxicity, with mucositis being a frequent reason for dose adjustment. The favorable side effect profile and convenience of administration of methotrexate make it well-suited for use in this patient population in which medical comorbidity is common, as is more advanced age. In randomized trials, higher doses increase response rates and toxicity without a significant improvement in overall survival.[66,67] Newer analogs of methotrexate (e.g., edatrexate) have not been shown to offer a therapeutic advantage in phase III trials.[68]

Cisplatin is a cornerstone drug in the modern management of head and neck cancer. Cisplatin is customarily dosed at 75 to 100 mg/m^2 intravenously every 3 to 4 weeks. The potential for renal (i.e., increase in creatinine, electrolyte abnormalities), otologic (i.e., high frequency hearing loss, tinnitus), neurologic (i.e., peripheral neuropathy), and gastrointestinal (i.e., nausea and vomiting) toxicity are widely appreciated, but these risks are manageable if patients are appropriately screened for therapy, monitored closely, and state of the art supportive care measures are applied. Further dose escalation of cisplatin has not been established to improve outcome. A randomized trial comparing 60 mg/m^2 versus 120 mg/m^2 of cisplatin failed to demonstrate a significant improvement in response or survival.[69] Carboplatin is the best studied and most commonly used platinum analog in head and neck cancer. Although generally less toxic and easier to administer than the parent drug, it is more bone marrow suppressive and may be somewhat less active. This last issue is more of a concern in the definitive treatment setting in which cure is a central endpoint, as opposed to the palliative setting, when patients often seek a less toxic alternative treatment.

Although taxanes as a class have significant activity in head and neck SCCs, hopes of clinically significant improvement in survival in the palliative setting with the introduction of these agents have yet to be realized. Neither paclitaxel or docetaxel has been demonstrated in random assignment trials to be clearly superior to methotrexate with regard to survival as an endpoint.[70] Paclitaxel dosed at 250 mg/m^2 intravenously over 24 hours with growth factor support in an Eastern Cooperative Oncology Group (ECOG) trial, yielded a major response in 12 of 30 patients (40%) including

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four complete responses; grade 3 or greater neutropenia occurred in 91% of patients, and there were two deaths.[71] Less cumbersome to administer and less toxic schedules are commonly used in practice (e.g., 135 to 225 mg/m^2 intravenously over 3 hours every 3 weeks; 80 to 100 mg/m^2 weekly), although their relative efficacies have not been well evaluated. A paclitaxel schedule that provides more prolonged exposure to the drug may be more efficacious,[72] although a phase II trial of 120 to 140 mg/m^2 over 96 hours yielded disappointing results even in treatment-naïve patients (major response rate, 13%).[65] Other toxicities besides myelosuppression include sensory neuropathy, alopecia, allergic reactions, and arrhythmia, although cardiac monitoring is not required.

Docetaxel appears less neuropathic than paclitaxel, but fluid retention and hematologic toxicity may be more problematic. A typical dose is 60 to 100 mg/m^2 intravenously over 1 hour. Initial studies evaluated the efficacy of the 100 mg/m^2 dose level, with major response rates ranging from 21% to 42%[73]; an excellent performance status is required for this higher dose. Lower doses may offer similar efficacy and better tolerance.[74] As with paclitaxel, weekly schedules are applied in practice, but the relative efficacy of weekly versus a schedule of every 3 weeks is not well-studied.

Although initial studies evaluated a bolus schedule for 5-fluorouracil, an infusional program of 1,000 mg/m^2 per day over 96 to 120 hours appears more efficacious in head and neck cancer.[75] Infusional 5-fluorouracil is associated with more mucositis and diarrhea than a bolus schedule, so the shorter infusion (i.e., 96 hours) is typically applied in patients who are pretreated and have received prior head and neck RT.

EGFR is highly expressed in most head and neck SCCs, and the degree of expression is inversely associated with prognosis.[76–78] As such, there has been a keen interest in drugs that target the receptor itself or steps downstream. Cetuximab, a chimeric immunoglobulin G antibody that binds the receptor, has been approved by the U.S. Food and Drug Administration for use in patients with disease refractory to platin-based therapy. As summarized in Table 38.7, the response rates in this refractory setting are similar (10% to 13%) whether cetuximab is used alone or combined with platin-based therapy; median survivals remained disappointing, ranging from 5.2 to 6.1 months.[79–82] Another EGFR antibody, zalutumumab, was compared in a randomized trial to best supportive care alone in patients with cisplatin-refractory squamous cell head and neck cancer. Among 286 entered patients, there was no significant improvement in the primary endpoint of overall survival (median 6.7 versus 5.2 months, p = 0.0648) although a significant difference was found on an exploratory post hoc analysis done 12 months after the last patient was randomized. Response rate (6.3% versus 1.1%) and progression-free survival (median 9.9 versus 8.4 weeks, p = 0.0012) were improved with zalutumumab.[83]

The small molecule tyrosine–kinase inhibitors, gefitinib and erlotinib, offer no efficacy advantage in similar refractory patients. Major response rates and median survivals ranged from 0% to 15% and 5.9 to 8.1 months, respectively.[78,84–86] A large randomized trial (486 patients) compared gefitinib (250 or 500 mg daily) to methotrexate and demonstrated no survival improvement with either gefitinib dose.[87]

With both of these classes of agents, the development of rash was associated with clinical benefit, but this association is not fully explained by simple pharmacokinetics.[78] There is no established molecular predictor of response to these agents currently in head and neck SCC.

The successful development and approval of cetuximab in head and neck SCC highlights the potential for therapies to exploit specific molecular pathways with therapeutic effect. A number of other new agents, often with multitarget capability, are entering clinical trials. There is a good rationale for agents that target angiogenesis in head and neck SCC.[88] However, the development of bevacizumab has been cautious given the reported toxicity concerns, specifically bleeding, in patients with squamous cell lung cancer.[89] Alterations in the PI3K/Akt/mammalian target of rapamycin (mTOR) pathway are common in head and neck cancer, and activation appears independent of EGFR activation, making targeting of this pathway of great interest.[90] Cancer gene therapy, whereby genetic sequences are introduced via viral or nonviral vectors, is well-suited to head and neck tumors given the local–regional character of head and neck tumors that facilitates direct injection and the monitoring of gene expression. The tumor suppressor gene p53 has been one target, because somatic mutations of it are common in head and neck cancers, particularly among patients who have smoked cigarettes and used alcohol.[91] For example, in a phase II study of Onyx-015, a replication-competent adenovirus absent the E1B gene, major responses, including some complete regressions, occurred in 10% to 14% of treated patients.[92] In other studies, treatment with Onyx-015, or a similar virus such as H101, improved the efficacy of chemotherapy.[93,94]

Combination Therapy

Given the disappointing track record for single-agent therapy in the palliative setting, combinations of drugs have been extensively evaluated. In the early 1980s, investigators from Wayne State, building upon potential synergy between cisplatin and 5-fluororuacil, reported a major response rate of 70% with a complete response rate of 27% using a regimen of cisplatin 100 mg/m^2 intravenously and a 5-fluorouracil 1,000 mg/m^2 per day continuous infusion over 96 hours recycled every 3 weeks in patients with recurrent or disseminated disease.[95] Other investigators confirmed the significant activity of the regimen, albeit with a somewhat lower major and complete response rate on average (50% and 16%, respectively),[96] establishing it as the standard regimen to which new therapies are compared.

TABLE 38.7

Cetuximab for Recurrent or Metastatic Head and Neck Cancer: Selected Studies

Author	No. of Patients	Cancer	Chemotherapy	RR	Median PFS (Months)	Median OS (Months)
Herbst et al.[80,a]	79	SCC–POD on CDDP based	CDDP based + cetuximab	6%–20%	2.0–3.0	4.3–6.1
Baselga et al.[79,a]	96	SCC–POD on platin based	CDDP based + cetuximab	10%–11%	2.4–2.8	4.9–6.0
Trigo et al.[81]	103	SCC–POD on platin based	Cetuximab	13%	2.3	5.9
Burtness et al.[82,b]	117	SCC No chemo for R/M	CDDP CDDP + cetuximab	10% 26%	2.7 4.2	8.0 9.2

[a] Range related to how POD was defined in different subgroups.
[b] Response rates were significantly different (p = 0.03): PFS (p = 0.09) and OS (p = 0.21) did not reach statistical significance.
RR, response rate; PFS, progressive-free survival; OS, overall survival; SCC, squamous cell cancer; POD, progression of disease; CDDP = cisplatin; R/M = recurrent or metastatic disease.

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Despite an improvement in response rates associated with the use of combination therapies like cisplatin and 5-flurouracil, demonstrating a statistically or clinically significant improvement in survival compared to single-agent therapy has proven elusive. Table 38.8 summarizes the results of three randomized trials that compared treatment with cisplatin and infusion 5-fluorouracil to that with different single agents.[97–99] Treatment with combination chemotherapy led to a significant increase in response rate, albeit at the cost of greater toxicity. Overall survival did not significantly improve. The meta-analysis reported by Browman et al.[100] yielded similar conclusions. These data do not support the routine use of cisplatin-based combinations for patients with recurrent or metastatic SCC. Combination therapy seems most appropriate for patients with a good performance who have significant symptoms (e.g., pain) for which the higher anticipated response rate will translate into better palliation.

The activity of paclitaxel and docetaxel in head and neck cancer has fostered the development and evaluation of taxane and cisplatin combinations. Docetaxel with cisplatin is associated with a major response rate of 40% to 53%, with complete response rates approximating 6% to 18%[101,102]; a weekly schedule of paclitaxel (80 mg/m^2) and carboplatin (area under concentration [AUC] versus time curve, 2) appeared more efficacious than an every 3-week dosing (paclitaxel 175 to 200 mg/m^2 intravenously over 3 hours followed by carboplatin AUC 6) in two separate phase II studies.[103–105] ECOG compared a high-dose (200 mg/m^2) and moderate-dose (135 mg/m^2) paclitaxel, both by 24-hour infusion and followed by the same dose of cisplatin (75 mg/m^2) in a randomized study (E1393). No significant difference in response rate or survival was found between the arms.[106] Another randomized trial done under the auspices of ECOG compared standard cisplatin and 5-fluorouracil with paclitaxel 175 mg/m^2 intravenously over 3 hours and cisplatin 75 mg/m^2 (E1395).[107] Objective major response rates (27% versus 26%) and median survivals (8.7 versus 8.1 months) were no different between the arms. The reported quality of life was better on the paclitaxel arm over the first 16 weeks of treatment.[108]

Attempts have been made to improve the efficacy of combination chemotherapy through the development of a variety of triplets. The addition of interferon-alpha2b (IFN-α2b) to cisplatin and 5-fluorouracil failed to significantly improve response or survival in a randomized trial.[109] Phase II studies of a taxane with cisplatin or carboplatin and a third drug (e.g., 5-fluorouracil, ifosfamide), have yielded major response rates of 55% to 86%[110–113]; whether these regimens translate into better survival outcomes compared to a cisplatin-based doublet that may be less toxic await further evaluations.

There is great interest in the combination of standard chemotherapy with newer targeted agents. One ECOG study compared cisplatin versus cisplatin and cetuximab as first-line treatment in 123 patients. The arm including the cetuximab had a significantly higher response rate (10% versus 26%, p = 0.03), but no significant difference was found in the primary endpoint of progression-free survival (2.7 versus 4.2 months, p = 0.09) or in overall survival (8.0 versus 9.2 months, p = 0.21), although the trends favored the combination arm.[82] In a larger trial (EXTREME),[114] 442 patients were randomized to cisplatin or carboplatin and 5-fluorouracil with or without cetuximab for six cycles. Subsequent maintenance with cetuximab alone was allowed on the investigational arm, but there was no crossover to cetuximab on the standard arm. Both median progression-free (5.6 versus 3.3 months) and overall (10.1 versus 7.4 months) survivals were significantly improved on the triplet arm, at the cost of more sepsis (nine patients versus one patient; p = 0.02), grade 3 skin reactions (9%), and grade ≥3 infusion reactions. Quality of life outcomes were reported to not be significantly different between the treatment arms.[115] Tumor EGFR copy number and degree of EFGR expression were not predictive of benefit with cetuximab.[116,117] Of interest, data from Vermorken and colleagues[118] suggests that the therapeutic effect of cetuximab, when combined with chemotherapy, is mainly additive rather than synergistic. Whether allowing patients to crossover to cetuximab on the doublet arm at progression would have decreased or eliminated the observed survival difference is of interest for future research. A similar but not identically designed randomized trial evaluated cisplatin and 5-flourouracil with or without the EGFR antibody panitumumab in 657 patients. Response rate (36% versus 25%, p = 0.0065) and median progression-free survival (5.8 versus 4.6 months, p = 0.0036) were significantly improved with the incorporation of the panitumumab, but not the primary endpoint of overall survival (11.1 versus 9.0 months, p = 0.1403). Overall survival was improved in the p16-negative subgroup (p = 0.0115).[119]

With advances in RT techniques that facilitate reirradiation with acceptable morbidity, this approach has been increasingly

TABLE 38.8

Chemotherapy for Recurrent or Metastatic Head and Neck Cancer: Selected Phase III Trials of Cisplatin/5-Fluorouracil Versus Other Options

Study	No. of Patients	Agents	Response Rates[a]	Median Survivals[b] (Months)
Jacobs et al.[98]	249	CDDP/FU CDDP FU	32% 17% 13%	5.5 5.0 6.1
Forastiere et al.[97]	277	CDDP/FU CBDCA/FU MTX	32% 21% 10%	6.6 5.0 5.6
Clavel et al.[99]	382	CDDP/MTX/BLEO/VCR CDDP/FU CDDP	34% 31% 15%	8.2 6.2 5.3
Schrijvers et al.[109]	122	CDDP/FU/IFN-α2b CDDP/FU	38% 47%	6.0 6.3
Gibson et al.[107]	218	CDDP/FU CDDP/PAC	27% 26%	8.7 8.1

[a] The following response rate differences were statistically significant at p <0.05: Jacobs et al., CDDP/FU versus both CDDP and FU; Forastiere et al., CDDP/FU versus MTX; Clavel et al., both combinations versus CDDP.
[b] All survival differences were not statistically significant.
CDDP, cisplatin; FU, 5-fluorouracil; MTX, methotrexate; CBDCA, carboplatin; BLEO, bleomycin; VCR, vincristine; IFN-α2b, interferon-alpha 2b; PAC, paclitaxel.

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explored in patients with unresectable local or regional recurrence, often with integrated chemotherapy. The observed median survivals in these series are similar to those obtained in phase II trials of chemotherapy alone, but more durable responses occur in selected patients and there is a clearer plateau on the survival curve. In two larger series involving 169 and 115 patients, respectively, among patients treated with a variety of RT fractionation schedules and concurrent chemotherapy regimens, 2-year survival rates exceeded 20%.[120,121] In two sequential RTOG studies, a regimen of daily paclitaxel (20 mg/m^2) and cisplatin (15 mg/m^2) added concurrently to split-course RT (total dose 60 Gy, 1.5 Gy twice-daily fractions; granulocyte colony-stimulating factor support during off weeks) (RTOG 96-11) yielded a better 2-year survival rate than concurrent 5-fluororuacil and hydroxyurea added to the same RT schedule (RTOG 96-10) (24.9% versus 16.9%, p = 0.44).[122,123] The reported 2-year survival rates exceed the rate of 10.5%, which was observed in a subgroup of 124 patients with local disease only who had previously received RT and participated in E1393 or E1395.[124] Randomized trials comparing chemotherapy alone to reirradiation and chemotherapy are needed.

Nasopharynx Cancer

Many of the same drugs and regimens used in the treatment of head and neck SCC are also active in NPC. There are reports of a small proportion of patients with recurrent or metastatic disease being controlled long term with chemotherapy alone.[125] Available data support the use of cisplatin-based combination chemotherapy (e.g., cisplatin/5-fluorouracil; cisplatin/bleomycin/5-flurouracil +/− epirubicin), although there is a lack of randomized studies to clarify the relative efficacies and toxicities of different options. Site-specific phase II studies report major response rates of 70% or higher with regimens containing cisplatin.[126–128] In a review of the Princess Margaret Hospital experience, single-agent or noncisplatin-based combination chemotherapy was associated with a major and complete response rates of 25% and 8%, respectively, in 40 patients, whereas cisplatin-based combination therapy produced major and complete response rates of 70% and 23%, respectively, in 30 patients.[126] The substitution of carboplatin may be associated with less activity.[127]

With regard to other agents, paclitaxel as a 175 mg/m^2 3-hour infusion is active with a response rate of 22% in a series of 24 patients with undifferentiated NPCs.[128] The combination of it with carboplatin has yielded response rates consistently greater than 50%.[129–131] Gemcitabine is active in NPCs,[132,133] and combinations including it appear promising, with response rates exceeding 70%.[134,135] Capecitabine, prolonged 5-fluorouracil infusion, and cetuximab all have modest activity in the refractory setting, and no major responses were seen in one study with gefitinib.[136–139] There is keen interest in looking to exploit the association NPCs have with EBV for therapeutic purposes. Potential gene therapy approaches are discussed elsewhere.[140,141]

GENERAL PRINCIPLES OF COMBINING MODALITIES

Surgery Plus Radiation Therapy

RT may be administered preoperatively or postoperatively. An analysis of available data suggests there is no compelling difference in survival rates comparing the two sequences[42]; local–regional control may be improved with postoperative treatment.[142]

Combined modality therapy should be avoided for lesions with a high cure rate (70% or greater) by either surgery or RT alone. The increased morbidity from combined treatment is not associated with a significantly improved control rate, and many patients with local or regional failure can be salvaged by secondary procedures.

The advantages of postoperative compared with preoperative RT include less operative morbidity, more meaningful margin checks at the time of the surgery, a knowledge of tumor spread for RT planning, safe use of a higher RT dose, and no chance the patient will refuse surgery. The disadvantages of postoperative RT include the larger treatment volume necessary to cover surgical dissections, a delay in the start of RT with possible progression, and the higher dose required to accomplish the same rates of local–regional control.

Preoperative Radiation Therapy

Preoperative RT should be considered for the following situations: (1) fixed-neck nodes, (2) delayed initiation of postoperative RT by >8 weeks, (3) use of the gastric pull-up for reconstruction, and (4) open biopsy of a positive neck node.

Postoperative Radiation Therapy

Postoperative RT is considered when the risk of recurrence above the clavicles exceeds 20%. The operative procedure should be one stage and of such magnitude that RT is started no later than 6 to 8 weeks after surgery. The operation should be undertaken only if it is believed to be highly likely that all gross disease will be removed and margins will be negative.

Although no definitive randomized trials have addressed the efficacy of postoperative RT in the treatment of head and neck cancer, excellent data that has bearing on this issue is available from the Medical College of Virginia. Two groups of surgeons operated on patients with head and neck cancer: general surgical oncologists who used surgery alone and reserved RT for treatment of recurrent disease, and otolaryngologists who routinely sent patients with locally advanced disease for postoperative RT.[143] Of 441 patients, 125 were treated surgically between 1982 and 1988 and had ECE and/or positive margins, 71 were treated with surgery alone, and 54 received postoperative RT. Local control rates at 3 years after surgery alone compared with surgery and RT were: for ECE, 31% and 66% (p = 0.03); positive margins, 41% and 49% (p = 0.04); and ECE and positive margins, 0% and 68% (p = 0.001). A multivariate analysis of local control revealed that the use of postoperative RT (p = 0.0001), macroscopic ECE (p = 0.0001), and margin status (p = 0.09) were of independent significance. Cause-specific survival rates at 3 years were 41% for surgery alone and 72% for surgery and postoperative RT (p = 0.0003). A multivariate analysis of cause-specific survival showed that postoperative RT (p = 0.0001) and the number of nodes with ECE (p = 0.0001) significantly influenced this endpoint.

In another series, Lundahl et al.[144] reported on 95 patients with node-positive SCC who were treated with a neck dissection and postoperative RT at the Mayo Clinic. A matched-pair analysis was performed using a series of patients treated with surgery alone; 56 matched pairs of patients were identified. The recurrence rates in the dissected neck (relative risk [RR] = 5.82, p = 0.0002), recurrence in either side of the neck (RR = 2.21, p = 0.0052), and death from any cause (RR = 1.67, p = 0.0182) were significantly higher for patients treated with surgery alone.

Thus, it appears that postoperative RT may significantly improve both local–regional disease control and survival for patients who are at high risk for failure after surgery.

Indications for postoperative RT include close (<5 mm) or positive margins, ECE, multiple positive nodes, invasion of the soft tissues of the neck, endothelial-lined space invasion, PNI, and more than 5 mm of subglottic invasion.[42] The authors currently recommend 60 Gy in 6 weeks to 66 Gy in 6.5 weeks for patients with negative margins and fewer than three indications for RT. For patients with close (<5 mm) or positive margins, we recommend 70 Gy in 7 weeks or 74.4 Gy at 1.2 Gy twice a day. Concomitant cisplatin chemotherapy should be considered for patients with positive margins and/or ECE.[43–45]

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Given the appreciation that HPV-related cancers have a better prognosis than HPV-unrelated disease, there is interest in potential deescalation of therapy with the intent of decreasing toxicity without compromise in survival.[145] Although this is an important area of future research, modification in standards of care based on the HPV status of the tumor is not recommended outside of a clinical trial at present.[146]

CHEMOTHERAPY AS PART OF CURATIVE TREATMENT

Systematically designed and randomized studies have established a role for drug therapy as part of the standard combined modality management of head and neck SCC in several settings. These include the therapy of unresectable disease, for organ preservation, and for patients with poor risk pathologic features after surgery. Chemotherapy has been shown to improve the likelihood of disease control compared to RT alone in patients with advanced disease, albeit with increased acute toxicity. In certain circumstances, response to chemotherapy has been used to triage patients to different local–regional treatments.

Chemotherapy has been integrated with surgery or RT in a variety of ways including induction, concurrent with RT, and/or maintenance. Unlike outcome studies of surgery and/or RT in which site-specific results are reported, albeit typically using a retrospective methodology, many of the trials evaluating the role of chemotherapy enrolled patients with a variety of head and neck SCCs. Even when site specific, although prospective, subsites are combined. This is less of an issue for studies evaluating therapy for NPC.[147,148] Nonetheless, important lessons have been learned from these studies, further enhanced by use of a random assignment methodology. In this section, general principles for the integration chemotherapy with local–regional treatment will be discussed with a focus on the results of randomized trials.

The Meta-Analysis of Chemotherapy on Head and Neck Cancer (MACH-NC) included 63 randomized trials published from 1965 through 1993, all of which compared local–regional treatment with or without chemotherapy.[149] Individual patient data was available on 10,741 patients. The absolute improvement in 5-year survival overall was 4% ($p < 0.001$). However, the significant improvement appeared limited to those patients who received concomitant treatment (absolute difference of 8% at 5 years, $p < 0.001$). Neither the difference seen at 5 years with induction (2%, $p = 0.10$), nor maintenance (1%, $p = 0.74$) chemotherapy was statistically significant.[149] In an update of this analysis, now including trials through 2000 and totaling 17,346 patients,[149] the superior efficacy of concurrent therapy was confirmed, and was greater than that seen with induction chemotherapy. Survival benefit diminished with patient age and, on subset analysis, was not significant in patients over 70 years of age.

Tumor HPV status has emerged as an important predictor of favorable treatment response and survival, particularly for patients with oropharynx cancer.[7] In ECOG 2399, the response to chemotherapy to all protocol treatment, progression free-survival, and overall survival were all improved in the HPV-positive group.[7] Subsequent analysis of RTOG 0129 demonstrated that tobacco use (>10 pack-years) and the extent of nodal disease (N2b-N3) both adversely affect the prognosis associated with HPV-positive tumors.[8]

Induction Chemotherapy

In untreated patients with local or regionally advanced M0 head and neck SCC, treatment with cisplatin-based combination chemotherapy will yield major response rates approximating 90%, with clinical complete response rates in the 30% range.[150] Enthusiasm that response rates of this magnitude should translate into survival benefit when induction chemotherapy was combined with surgery or RT is understandable. Yet, in the original report of the MACH-NC analysis, which included 31 induction studies, all but 2 suggested no survival benefit.[149]

However, a more careful look at these and other data do provide grounds for continued interest in this approach. Many of the included studies had significant methodologic limitations by more contemporary trial standards. A subset analysis, limited to the 15 trials that used cisplatin and infusional 5-fluorouracil, suggested survival benefit (hazard ratio [HR], 0.88; 95% confidence interval [CI], 0.79 to 0.97).[149] Even in the absence of survival improvement, there seemed to be a correlation between response to chemotherapy and subsequent response to RT, which provided a basis for subsequent organ preservation initiatives.[151,152] Finally, patterns of failure were affected with less distant metastases in certain studies when induction chemotherapy was incorporated. As local–regional control improves, the rate of clinically apparent distant metastases is increasing,[153] and induction chemotherapy is, on average, better tolerated than maintenance therapy as a way to give additional systemic therapy.

The study reported originally by Paccagnella et al.[154] is illustrative of these types of trials, and provides further insights.[155] Two hundred and thirty-seven patients with stage III or IV head and neck cancer were randomized to four cycles of induction cisplatin and infusional 5-fluorouracil followed by standard local–regional treatment (i.e., surgery plus RT if resectable, RT alone if unresectable). Resectability was assessed pretreatment, not after chemotherapy, and was a stratification criteria. Overall, there was no significant difference between the arms with regard to overall survival or local–regional control, although the incidence of distant metastases was lower among patients treated with chemotherapy. On a subset analysis, however, patients with unresectable disease benefitted from the incorporation of induction chemotherapy for all outcomes, including local–regional control, distant control, and overall survival (3-year survival 24% versus 10%, $p = 0.04$). Among resectable patients, improvement in distant control was offset by a decrement in local–regional control with the integration of induction chemotherapy, and reported survival rates in this subgroup were similar on both treatment arms.

Historically, then, there was no established role for induction chemotherapy prior to planned surgery and postoperative RT, and a limited role only in selected settings prior to RT. However, with the incorporation of taxanes into induction regimens containing cisplatin and 5-fluororuacil, newer data suggest that the indications for induction chemotherapy may further evolve.

Three randomized trials have compared the relative efficacies of induction chemotherapy with standard cisplatin and 5-fluorouracil versus a triplet including a taxane and these same two drugs with one or both being dose adjusted.[156–158] All three studies randomized patients with advanced M0 head and neck cancer to either cisplatin and 5-fluororuacil or a triplet, followed by the same RT-based treatment. In one study, this was RT alone, whereas, in the other two, concurrent therapy with carboplatin and cisplatin, respectively, were employed. In general, the taxane-containing triplet was associated with a higher response rate to induction chemotherapy, and improved both progression-free and overall survival. More neutropenia was observed with triplet therapy but, overall, it was as well-tolerated as standard cisplatin and 5-fluorouracil.

These studies were designed to determine which induction chemotherapy was more efficacious, and provide convincing evidence that the triplet of a taxane with cisplatin and 5-flurouracil is superior to standard cisplatin and 5-fluorouracil alone as induction therapy. However, an alternative design is necessary to define the role of induction with such triplets in standard practice. For this population, as discussed in the next section, concurrent chemotherapy and RT alone without induction chemotherapy is the more established standard therapy. Randomized studies are necessary to determine whether a sequential approach using induction with a

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triplet followed by RT-based treatment (typically with concurrent chemotherapy), is superior to concurrent chemotherapy and RT alone such that the added duration of treatment and potential toxicity is justified.

To date, available randomized trials have failed to demonstrate a clear overall survival benefit with the incorporation of induction chemotherapy. The combination of docetaxel, cisplatin, and 5-fluorouracil has been the focus of these investigations. One study available only in abstract form was confounded by the lack of an intention to treat an analysis with unequal exclusions among treatment arms. Even with those methodologic limitations, it failed to demonstrate a significant improvement in overall survival with the incorporation of induction docetaxel, cisplatin, and 5-fluorouracil or cisplatin, and 5-fluorouracil.[159] In the PARADIGM study, 145 patients with local or regionally advanced SCC were randomized to induction docetaxel, cisplatin, and 5-fluorouracil followed by carboplatin or docetaxel concurrent with RT versus concurrent cisplatin with concomitant boost radiation. Patients could have unresectable disease or be resectable, with the intent of therapy being organ preservation. The study was closed early because of slower than expected accrual, so it was somewhat underpowered. There was no difference in overall or progression-free survival between the arms with a median follow-up of 49 months; the 3-year overall survival rates were 73% on the induction arm and 78% on the concurrent arm ($p = 0.77$); and the 3-year progression-free survival rates were 67% and 69%, respectively ($p = 0.82$). A subset analysis of the group with advanced neck disease (N2b/N2c,N3), felt to be at increased risk of distant metastases, demonstrated no advantage with the incorporation of induction chemotherapy.[160] The DECIDE trial used a similar design, but only patients with N2/N3 were eligible and, for the concurrent therapy, hydroxyurea and 5-fluorouracil was used. Among 280 patients accrued with minimum 24-months follow-up, there was no significant difference between the sequential and concurrent arms with regard to overall survival (75% versus 73%, $p = 0.70$) or disease-free survival (69% versus 64%, $p = 0.39$); the cumulative incidence of distant failure, however, was lower in the induction arm (10% versus 19%, $p = 0.025$).[161] Finally, in 256 enrolled patients with stage III or IVA oral cavity cancer, induction with docetaxel, cisplatin, and 5-fluorouracil prior to surgery and postoperative radiation failed to improve overall survival ($p = 0.918$) or disease-free survival ($p = 0.897$) compared to proceeding directly to surgery and postoperative radiation alone.[162]

The optimal role of induction chemotherapy is currently controversial. A review of the National Comprehensive Cancer Network (NCCN) guidelines highlights this reality, because concurrent chemoRT alone and induction followed by RT-based therapy are both listed as treatment options for certain disease scenarios.[146] Although concurrent chemoRT alone remains the standard to which new treatments are compared for local or regionally advanced disease and generally receives the higher category rating in these guidelines, induction is well-suited for certain settings in patients who are medically fit. Examples include when immediate therapy is needed in the hope of avoiding a tracheostomy or PEG, in organ preservation settings where the degree of response affects the decision to proceed with surgery versus RT-based therapy, or in patients with advanced neck disease at higher risk for distant metastases.

After induction chemotherapy, there is some controversy as to whether to proceed with RT alone or concurrent chemoRT, and if the latter, which drug to use.[156–158] Concern exists regarding the tolerance to high-dose cisplatin after cisplatin-based induction treatment. In a randomized phase II trial, concurrent cetuximab and RT was compared with high-dose cisplatin and RT after induction docetaxel, cisplatin, and 5-fluorouracil in 116 patients with advanced hypopharynx or larynx cancer. Toxicity was substantial on both arms, but treatment compliance was better with cetuximab therapy. There was no significant difference in larynx function preservation and overall survival between the arms; more local failures occurred on the cetuximab arm.[163]

Concurrent Chemotherapy and Radiation for Gross Disease

Although there are a number of ways to integrate chemotherapy with RT, available data most strongly support concurrent chemotherapy. Given proven efficacy in patients with poor prognostic and unresectable disease, more recent investigations have applied the approach in better prognostic, organ preservation, and adjuvant settings.

Concurrent chemoRT programs vary in many ways, of which the type of chemotherapy (i.e., specific agents, single, combination) and RT schedule (i.e., dose, fractionation) are the most apparent variables. In general, three main approaches can be discerned: single-agent or combination chemotherapy with continuous-course RT; combination chemotherapy with split-course RT, often with altered fractionation; and chemotherapy alternating with RT.[164] Although continuous course RT may be desirable and more attractive from a radiobiologic perspective, local toxicities may preclude it depending on the concurrent agents used. The first two approaches are the most common.

A variety of drugs and combinations have been utilized concurrently with RT. When only one drug is used, the MACH-NC indicates that the impact is largest with a platin, of which cisplatin is the predominant one studied, a conclusion shared in another meta-analysis reported by Browman and colleagues.[165] Of interest, platin plus 5-fluorouracil (HR, 0.75) offered no clear advantage compared to platin alone (HR, 0.74).[166] The results of a three-arm randomized study comparing concurrent cisplatin and RT, concurrent cisplatin, 5-fluorouracil and split-course RT (with possible resection depending on response), and definitive RT alone in patients with unresectable disease reported by Adelstein et al.,[167] in the E1392 study, are consistent with this assessment. Although daily,[168] weekly,[46,169] and every 3 week schedules of cisplatin intravenously concurrent with RT have been applied, the last schedule is the one most studied and is a widely accepted standard. If weekly dosing is used, 20 mg/m^2 weekly appears too low because it did not significantly improve overall survival or failure-free survival in one randomized study.[169] Attempts to improve the efficacy of concurrent cisplatin through intra-arterial administration[170,171] did not prove more efficacious in a randomized trial when compared to intravenously delivered cisplatin, although toxicity profiles differed.[172] In absence of a proven efficacy advantage with intra-arterial delivery, intravenous cisplatin is preferred because it is logistically easier to administer.

Most randomized trials to date have compared chemoRT to RT alone. As such, studies evaluating the efficacy of different chemoRT programs are limited. For example, for purposes of the MACH-NC analysis, "platin" included both cisplatin and carboplatin. Yet the relative efficacy of these agents, when given concurrently, is not well-studied. In one three-arm randomized study by Jeremic et al.[168] using a daily schedule for each drug with RT and a control arm of RT alone, both the cisplatin (6 mg/m^2 per day) and carboplatin (25 mg/m^2 per day) arms appeared comparable, and superior in efficacy to RT alone. However, in a randomized study reported by the Hellenic Cooperative Oncology Group using an every 3 week schedule for each drug (cisplatin 100 mg/m^2, carboplatin AUC, 6), their equivalence seemed less clear.[173] The RTOG reported a randomized phase II study comparing three different chemotherapy regimens, all delivered concurrently with 70 Gy in 2 Gy fractions: ARM 1, cisplatin 10 mg/m^2 per day and 5-fluorouracil 400 mg/m^2 per day continuous infusion for the final 10 days of treatment; ARM 2, hydroxyurea 1 g every 12 hours and 5-fluorouracil 800 mg/m^2 per day continuous infusion every other week; or ARM 3, weekly paclitaxel 30 mg/m^2 and cisplatin 20 mg/m^2. Among 231 analyzable patients, 2-year disease-free and overall survival rates were for ARM

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1, 38.2% and 57.4%; for ARM 2, 48.6% and 69.4%; and for ARM 3, 51.3% and 66.6%, respectively.[174]

Because anemia may adversely affect the efficacy of RT, the integration of an appropriate hematopoietic growth factor has been investigated. In a multicenter, double-blind, randomized, placebo-controlled trial, the addition of erythropoietin 300 IU/kg three times weekly during postoperative RT was evaluated in 351 patients with head and neck SCC.[175] Although target hemoglobulin levels were reached in 82% of patients receiving erythropoietin compared to 15% receiving placebo, local–regional progression-free survival (adjusted RR, 1.62 [95% CI, 1.22 to 2.14]; p = 0.0008), local–regional progression (RR, 1.69 [CI, 1.16 to 2.47]; p = 0.007), and survival (RR, 1.39 [CI, 1.05 to 1.84]; p = 0.02) were all inferior on the erythropoietin arm. Consistent with the current FDA alert, an erythropoietin-stimulation agent is contraindicated during curative-intent RT-based therapy.[176] Transfusion then, is the preferred approach to address potential radiation resistance attributed to anemia, but a recent analysis of two randomized trials failed to demonstrate that prophylactic transfusion improved overall survival or other disease control endpoints.[177] Use of a hypoxic radiosensitizer represents another strategy to potentially address tumor hypoxia. The results of one meta-analysis were consistent with potential benefit[178]; recent randomized trials, however, have not been convincing in terms of improved disease control with such a strategy.[179,180]

An important question is whether the use of newer, more efficacious, and altered fractionated RT programs[181] obviates the benefits accrued with the addition of chemotherapy. A single institution study reported by Brizel et al.[182] compared a more aggressive RT schedule with or without concomitant 5-fluorouracil and cisplatin. Patients who underwent RT alone received 75 Gy in 60 twice-daily fractions; those who underwent concomitant chemotherapy received 70 Gy in 56 twice-daily fractions with a 7-day split. Chemotherapy consisted of two cycles of concomitant cisplatin 12 mg/m^2 per day and 5-fluorouracil 600 mg/m^2 per day each for 5 days, followed by two cycles of maintenance chemotherapy. Among the 116 patients included, chemoRT was associated with improved 3-year rates of local–regional control (70% versus 40%, p = 0.01), relapse-free survival (61% versus 41%, p = 0.08), and overall survival (55% versus 34%, p = 0.07). In another randomized study reported by Jeremic et al.,[183] the addition of daily cisplatin to hyperfractionated RT also leads to incremental benefits. The results of these studies are consistent with the MACH-NC analysis, which demonstrated significant HRs, that are consistent with benefits among patients receiving postoperative RT (HR, 0.79), conventional RT (HR, 0.83), or altered fractionated RT (HR, 0.73), suggesting a benefit for adding concomitant chemotherapy regardless of the type of RT schedule.[166]

Of note, the converse—once concurrent chemotherapy is added, does an altered fractionation RT schedule further improve outcome compared to that seen with standard fractionation—has not been established in randomized trials. Neither RTOG 0129 (standard versus concomitant boost RT both with concurrent high-dose cisplatin)[8] nor GORTEC 99-02 (accelerated RT with or without concurrent carboplatin and 5-flourouracil, standard fractionated RT with concurrent carboplatin and 5-flourouracil)[184] demonstrated improved overall survival with the incorporation of altered fractionated RT with concurrent chemotherapy versus standard fractionation with concurrent chemotherapy to justify the added logistical complexity and potential added toxicity.

For patients who are not cisplatin candidates, using a carboplatin-based program (e.g., carboplatin/5-fluorouracil)[147] or other concurrent programs that have different side effect profiles and that withstood the scrutiny of a randomized trial is recommended. There has been great interest in cetuximab and concurrent RT in this regard.[185] In a randomized study reported by Bonner et al.,[186] patients with local–regionally advanced head and neck cancer were randomized to RT alone (213 patients) or combined with weekly cetuximab dosed in a standard fashion (211 patients); median follow-up was 54 months. The median duration of survival was 49 months after combined therapy compared with 29 months after RT alone (p = 0.03). Other than an acneiform rash and infusion reactions, grade 3 or greater complications were similar in the two groups of patients. The results of this trial have been confirmed with longer follow-ups.[186] Patients with oropharynx cancer appeared to derive the largest benefit with the integration of cetuximab, suggesting that HPV-related disease may have an improved outcome with the use of this agent; other studies, however, suggest greater activity of EGFR-directed antibody therapy in HPV-negative disease.[114,119] Randomized data comparing cetuximab and RT to other chemoRT programs are not available. One RTOG study evaluating concurrent cisplatin and RT versus cetuximab and RT in patients with HPV-related cancers is currently in progress. Investigators at Memorial-Sloan Kettering reported a phase II trial of cisplatin and cetuximab concurrent with RT in patients with local–regionally advanced head and neck SCC. Efficacy was impressive, although there were toxicity concerns.[187] The RTOG completed accrual to a large randomized trial (RTOG 0522, n = 895 evaluable patients) intended to assess the efficacy and safety of this regimen compared to concurrent cisplatin and RT. With a median follow-up of 2.4 years among surviving patients, the incorporation of cetuximab failed to significantly improve 2-year progression-free survival (63% versus 64%, p = 0.66) or overall survival (83% versus 80%, p = 0.17), but mucosal and skin toxicity were increased.[188]

Choosing among the numerous concurrent programs can be difficult. In the NCCN guidelines,[146] concurrent cisplatin with RT is the preferred choice, although several other options are listed. It is important to emphasize that concurrent chemoRT may be associated with significant toxicity; treatment-related mortality, albeit infrequent (<5% in the cooperative group setting), may occur. Morbidity from chemotherapy (dependent on the agent chosen) and RT are possible, and there are both acute (e.g., mucositis, blood count suppression) and chronic (e.g., dry mouth, swallowing dysfunction, fibrosis) toxicities. Selected studies have begun to report long-term, not just acute, toxicities.[189] Appropriate infrastructure, an experienced multidisciplinary team, and a cooperative patient are necessary to optimize both efficacy and safety.

Nasopharynx Cancer

Current practice has been particularly affected by the Intergroup Study 0099 (Table 38.9).[190] In it, 147 patients with stage III or IV NPC were randomized to definitive RT (70 Gy, 35 fractions over 7 weeks) versus cisplatin 100 mg/m^2 intravenously on days 1, 22, and 43 concurrent with the same dose of RT followed by three planned cycles of cisplatin and infusional 5-fluorouracil. Although only 63% and 53% of patients received all the planned concurrent and maintenance treatments, respectively, local–regional control, distant control, progression-free, and overall survivals were all significantly improved with chemoRT.

One of the potential limitations of the Intergroup Study was how generalizable its results would be to endemic NPCs, because 24% of patients entered in the trial had World Health Organization (WHO) type I histology. However, subsequent reports of randomized trials in which WHO types II and III predominated have similarly shown a survival advantage with concurrent cisplatin-based concurrent chemotherapy without[191–193] or with maintenance chemotherapy.[194,195]

One relatively small randomized trial (n = 206) with a median follow-up of 26.3 months, suggested that weekly carboplatin dosed at 100 mg/m^2 concurrent with RT when compared to standard high-dose cisplatin, did not yield inferior disease-free or overall survival. Both arms received adjuvant platin and 5-fluorouracil.[196] However, another randomized study involving 408 patients who received concurrent carboplatin at AUC 6 every 3 weeks after induction chemotherapy failed to demonstrate an improvement

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TABLE 38.9

Selected Randomized Trials Evaluating Concurrent Chemoradiotherapy Versus Radiotherapy for Advanced Nasopharynx Cancer

Study	No. of Patients	Maintenance Chemotherapy	Treatment Arms	PFS[a,b] (p value)	OS[a] (p value)
Al-Saraff et al.[190]	147	Yes, on CDDP/RT arm	RT CDDP/RT	24% 69% (<0.001)	47% 78% (0.005)
Lin et al.[191]	284	No	RT CDDP/FU/RT	53% 72% (0.0012)	54% 72% (0.0022)
Chan et al.[198]	350	No	RT CDDP/RT	52% 60% (0.06)	59% 70% (0.049)
Wee et al.[194]	221	Yes, on CDDP/RT arm	RT CDDP/RT	53% 72% (0.0093)	65% 80% (0.0061)
Lee et al.[195]	348	Yes, on CDDP/RT arm	RT CDDP/RT	62% 72% (0.027)	78% 78% (0.97)

[a] Five-year rates for Lin et al. and Chan et al.; otherwise, 3-year rates.
[b] Disease-free rate provided for Wee et al., and failure-free rate for Lee et al.
PFS, progression-free survival; OS, overall survival; CDDP, cisplatin; FU, 5-fluorouracil; RT, radiation therapy.

in overall survival at 5 years or other disease outcomes compared to patients receiving radiation alone after the same induction regimen.[197]

Another limitation of the Intergroup Study was that it was not designed to delineate the proportional benefits of concurrent and maintenance chemotherapy. Although current NCCN guidelines recommend concurrent and maintenance chemotherapy in M0 patients with a more advanced disease based on the Intergroup experience,[146] in reviewing available data, the benefits of maintenance chemotherapy appear more controversial. As noted, other randomized studies have demonstrated a survival improvement with concurrent therapy alone.[191,198] Earlier randomized trials, summarized elsewhere, failed to demonstrate a survival benefit when either maintenance or induction chemotherapy was added to definitive RT.[199,200] Furthermore, a meta-analysis of updated individual patient data on 1,753 patients enrolled in eight randomized trials, besides confirming an absolute survival benefit of 6% at 5 years with incorporation of chemotherapy with RT (HR, 0.82, 95% CI, 0.71 to 0.91; $p = 0.006$), also reported a significant association between the timing of chemotherapy and overall survival ($p = 0.005$), with the largest benefit being attributed to concomitant therapy.[201] A recently reported randomized trial involving 508 patients with nonmetastatic, stage III to IV nasopharyngeal cancer failed to demonstrate a significant difference in 2-year failure-free survival, overall survival, local–regional failure-free survival, or distant failure-free survival after a median follow-up of 37.8 months. Of note, the direction of each of the previous endpoint comparisons favored the adjuvant arm, albeit not significantly so, with associated p values of 0.13, 0.32, 0.10, and 0.12, respectively.[202] A longer term follow-up of this trial will be of interest. Currently, the NCCN guidelines list both concurrent chemoRT followed by maintenance chemotherapy and concurrent chemoRT alone as treatment options for advanced disease, with the former having the higher category rating.[146]

Selected randomized studies have demonstrated evidence of a positive biologic effect with the use of induction chemotherapy, but no survival benefit has been documented.[200,203–205] Such promising results have engendered interest in the potential for enhanced efficacy with newer drugs and combinations. A randomized phase II trial evaluating induction with docetaxel and cisplatin prior to concurrent cisplatin and RT was consistent with a benefit compared with concurrent cisplatin and RT alone.[200] Programs incorporating newer taxane- and cisplatin-based triplet induction regimens warrant further study.[206] There is also interest in the role of plasma EBV–DNA assays as a way to assess disease and monitor response.[199]

Organ Preservation

Organ preservation therapy is intended to control disease without compromise in survival while optimizing function or cosmesis.[207] The term implies that the tumor is potentially resectable for cure, and that the morbidity from surgery is significant. Although conservation surgical procedures can achieve the same goals, the label of organ preservation is more commonly applied to nonsurgical approaches. In that regard, the role of chemotherapy integrated with RT is best established for more advanced primary tumors. In this setting, conservation surgical procedures become less feasible, and local control rates with RT alone are lower than seen with earlier stage disease.

Total laryngectomy is one of the surgical procedures most feared by patients.[208] Thus, larynx preservation has been a central focus of many organ preservation studies, including those that established integrated chemotherapy and RT as a standard organ preservation treatment option. Studies commonly focused on patients with advanced tumors of the larynx, hypopharynx, and oropharynx (particularly the base of tongue), in whom primary surgical management would jeopardize the voice box.[209]

Initial chemoRT approaches to larynx preservation utilized induction chemotherapy. The response to initial chemotherapy was used to triage patients to either definitive RT (a partial response or better at the primary site; surgery to the primary site was reserved for salvage) or primary surgical management (lower than a partial response). The randomized and landmark Veterans Administration (VA) Larynx Preservation Study demonstrated that such an approach could be pursued in patients with advanced laryngeal cancer without compromise in survival when compared to primary treatment with surgery and RT.[151] Over 60% of patients on the chemoRT arm avoided total laryngectomy. Among

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long-term survivors, patients treated on the chemoRT arm had better emotional well-being, were less depressed, and also reported less pain.[210]

A similarly designed randomized trial in patients with pyriform sinus and aryepiglottic fold tumors reported by the European Organization for Research and Treatment of Cancer (EORTC) confirmed these findings.[152] However, a small randomized study (n = 68) limited to patients with T3 disease with a fixed cord done by the Groupe d'Etude des Tumeurs de la Tete et du Cou (GETTEC) reported that survival was superior on the primary surgery arm (84% versus 69% at 2 years, p = 0.006).[211] When the MACH-NC performed a collective analysis of the VA, EORTC, and GETTEC studies, the rate of larynx preservation among survivors was 58%. A nonsignificant (6%) decrement in survival at 5 years was seen in the chemoRT group (39% versus 45%; pooled HR, 1.19; 95% CI, 0.97 to 1.46; p = 0.10).[149]

The data reviewed in the prior section highlighting the therapeutic benefits of a concurrent chemoRT relative to an induction or RT alone approach have obvious implications for the larynx preservation setting. RTOG 91-11 was designed to assess the impacts of adding chemotherapy to RT and its timing (concurrent versus induction) with regard to achieving larynx preservation. Four hundred and ninety-seven patients with larynx cancer were randomized to one of three arms: primary RT, 70 Gy to the primary site, 50 to 70 Gy to nodes; induction chemotherapy with cisplatin and infusional 5-fluorouracil for three cycles followed by RT in responders, surgery in nonresponders; and cisplatin 100 mg/m^2 on days 1, 22, and 43 concurrent with RT. Surgical salvage was an option on all three arms. The recently updated 10-year results are summarized in Table 38.10.[148,212] As anticipated, the rate of grade 3 or 4 mucosal toxicity was highest on the concurrent arm; however, this did not translate into more significant speech or swallowing impairment at 2 years compared to the other treatment arms. Noteworthy is that, although the larynx preservation rate and local–regional control was highest and statistically superior with concurrent treatment, there was no significant difference in overall survival rates among the arms. Deaths not attributed to larynx cancer were highest in the concurrent arm (30.8%) versus 20.8% on the induction arm and 16.9% in the RT alone group, raising concern regarding the long-term morbidity of concurrent therapy. However, late effects were similar among the groups, and there were no substantial differences in speech or swallowing function reported.[212]

In another randomized larynx-preservation study, induction chemotherapy followed by RT and alternating chemotherapy and RT approaches were compared in 450 patients with advanced larynx or hypopharynx cancer. Both treatment arms used cisplatin and 5-flourouracil and allowed surgical salvage. Overall and progression-free survival rates were similar on both arms. Survival with a functional larynx in place was higher with alternating chemoRT, although the difference was not statistically significant (median, 2.3 years versus 1.6 years; HR, 0.85; 95% CI, 0.68 to 1.06).[213]

Available randomized phase III data support a concurrent chemotherapy–RT strategy administered with organ preservation intent for patients with advanced oropharynx cancer. A phase III study from the Groupe d'Oncologie Radiothérapie Tête et Cou (GORTEC) demonstrated improved local–regional control (66% versus 42% at 3 years, p = 0.03) in patients with advanced oropharynx cancer who received concurrent chemotherapy (carboplatin and 5-fluorouracil) and RT (70 Gy) compared to RT alone.[147] A non–site-specific trial from the Cleveland Clinic, which included a high proportion of patients with advanced oropharynx cancer, yielded similar results.[214]

Although concurrent chemotherapy is the current cornerstone of organ preservation treatment of advanced disease, other paradigms deserve mention. In an Italian study, 195 patients with T2 to T4 oral cavity cancer were randomized to either primary surgical management or induction chemotherapy with cisplatin and 5-fluorouracil followed by a surgical procedure, which could be modified based on response. Overall survival was similar on both arms, but less postoperative RT was necessary (33% versus 46%) and fewer mandible resections were performed (31% versus 52%) on the chemotherapy arm.[215] As a further extension of this concept, Laccourreye and colleagues[216] have pioneered the selective observation without local–regional treatment of patients with laryngeal cancer who have a complete response to induction chemotherapy. Durable tumor control without the addition of surgery or RT has been reported in a small subset of patients with early stage tumors.[216] The University of Michigan has developed a larynx preservation program whereby the triage to RT-based treatment or surgery occurs after only one cycle of chemotherapy.[217] The intent is to improve survival and minimize morbidity through the timely selection of appropriate therapy, including referral to surgery if indicated. The implication is that induction chemotherapy has little other therapeutic benefit, and some patients who are slow to respond may be triaged unnecessarily to total laryngectomy.[218] Conversely, newer sequential strategies of induction chemotherapy followed by planned concurrent chemotherapy are looking to optimize both local–regional and distant control. Induction with more efficacious triplet chemotherapy, including a taxane combined with cisplatin and 5-fluorouracil, is already being incorporated into larynx preservation strategies with evidence of improved larynx preservation rates.[219]

Adjuvant Therapy after Surgery

The use of maintenance chemotherapy after the completion of local–regional treatment has been evaluated in several randomized trials, but with disappointing results. Suboptimal compliance

TABLE 38.10

Intergroup 91-11: Updated Results at 10 Years

RX Arms	No. of Patients	LP Rate	LRF	DMF[a]	DFS	OS
RT only	171	63.8% p <0.0012	47.2% p = 0.0015	76.0%[b]	14.8%[b]	31.2%[b]
Induction PF→RT	173	67.5% p = 0.005	48.9% p = 0.0037	83.4% p = 0.06	20.4% p = 0.06	38.8%[a] p = 0.29
Concurrent P/RT	171	81.7%[b]	65.3%[b]	83.9% p = 0.08	21.6% p = 0.04	27.5% p = 0.53

[a] Trend, p = 0.08 for induction versus concurrent arm.
[b] Comparison group.
RX, treatment; LP, larynx preservation; LRF, local-regional failure; DMF, distant metastatic failure; DFS, disease-free survival; OS, overall survival; RT. radiation therapy; PF, cisplatin/5-fluorouracil; P, cisplatin.
From Forastiere AA, Zhang Q, Weber RS, et al. Long-term results of RTOG 91-11: a comparison of three nonsurgical treatment strategies to preserve the larynx in patients with locally advanced larynx cancer. *J Clin Oncol* 2013;31:845–852.

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with maintenance treatment may in part explain the lack of benefit, because tolerance of chemotherapy can be poor after surgery and RT.[220] Despite these limitations and the lack of convincing survival benefit, patterns of failure were affected in selected studies, with a decrease in distant metastases, consistent with a biologic effect of chemotherapy.[220,221]

The results of Intergroup 0034 highlight these points. In this trial, 442 analyzable patients were randomized after definitive surgical therapy to either postoperative RT alone (50 to 60 Gy) or three cycles of standard dose cisplatin and 5-fluorouracil by infusion followed by the same RT-dosing scheme. The randomization was stratified by risk, with surgical margins less than 5 mm, cancer in situ (CIS) at the margins, and ECE being considered high-risk features. Overall, there was no significant difference in overall survival, disease-free survival, or local–regional control between the treatment arms, although there was a significant decrease in incidence of distant metastases on the investigational arm ($p = 0.03$). Interestingly, on a subset analysis, adjuvant chemotherapy had no significant impact in the low-risk group, but a more dramatic impact on survival and tumor control was seen among high-risk patients. Given the success of concurrent chemoRT as definitive treatment, its application in the adjuvant setting was a logical extension. A pilot study done by the RTOG demonstrated that concurrent high-dose cisplatin every 3 weeks with RT was feasible in the adjuvant setting.[222] Early randomized studies demonstrated an improvement in local–regional control with the incorporation of concurrent mitomycin.[223,224] A study comparing weekly cisplatin concurrent with postoperative RT versus RT alone with ECE, yielded a significant improvement in both local–regional control and survival with combined modality treatment.[46]

Two randomized studies, both published in 2004, have further clarified the indications for postoperative chemoRT in the poor risk adjuvant setting. RTOG 9501 and EORTC 22931 had very similar designs.[43–45,209] Patients were randomized after surgery if they had poor risk features to either standard postoperative RT alone (60 to 66 Gy, over 6 to 6.5 weeks, standard fractionation) or the same RT with three planned cycles of concurrent cisplatin at 100 mg/m^2 every 3 weeks. What constituted poor risk differed somewhat between the studies: the RTOG required the presence of two or more positive lymph nodes, ECE, or positive margins; the EORTC required ECE, positive margins, pT3 or pT4 with any N, N2, or N3 disease, level IV nodes or stage IV disease in patients with oral cavity or oropharynx primaries, PNI, or vascular embolism.[43–45] Both studies demonstrated a significant improvement in local–regional control and disease-free or progression-free survival with combined modality therapy. These improvements translated into a significant advantage in overall survival in the EORTC study ($p = 0.02$), but only a trend ($p = 0.19$) in the RTOG study. Neither study showed a significant impact on distant control with the addition of chemotherapy. Acute toxicity was greater with the addition of the cisplatin, but there was no difference in late toxicity.

A subsequent analysis of the EORTC and RTOG studies was performed to better understand which pathologic subgroups may benefit the most from the concurrent addition of cisplatin to RT.[203] Patients having evidence of ECE or a positive margin derived the largest benefit from combined modality adjuvant therapy. Conversely, patients in whom their only poor risk factor was two or more positive lymph nodes without ECE seemed to do just as well with RT alone. Long-term follow-up of RTOG 9501 yielded results consistent with this conclusion.[45]

The EORTC and RTOG studies focused on patients who were previously untreated with the exception of prior surgery. Janot et al.,[225] on behalf of the GETTEC and GORTEC groups, addressed the potential role of concurrent chemotherapy and reirradiation after salvage surgery. In this randomized study enrolling 130 patients, the standard arm was salvage surgery alone. The combined modality treatment significantly improved disease-free survival (HR, 1.68 [95% CI, 1.13 to 2.5], $p = 0.01$), although overall survival was not significantly improved and both acute and chronic toxicities were worse.

Some investigators have questioned whether extracapsular nodal spread has the same adverse prognostic implications in patients with HPV-related disease.[226] The related therapeutic question is whether this pathologic risk factor should drive the addition of concurrent chemotherapy to radiation in the postoperative setting for patients with HPV-related disease. These issues are the focus of ongoing investigations. For now, the NCCN does not recommend different approaches to treatment in the poor-risk adjuvant setting based on tumor HPV status.[146]

Toxicity Reduction

Xerostomia is one of the most troubling side effects of RT-based treatment. Extra oral fluids, artificial saliva, other topical measures, and humidity are commonly utilized. Available data indicates that IMRT applied with salivary-sparing intent decreases this symptom.[34,227,228] Historically, the emphasis has been on parotid sparing. Sparing other salivary glands when possible further improves salivary outcomes.[229,230] Pharmacotherapy may also help. The cholinomimetic and muscarinic agent, pilocarpine, at a dose of 5 mg three times a day was shown in a randomized trial to improve the production of saliva as well as symptoms of dry mouth compared to placebo in patients treated with at least 40 Gy to the head and neck.[231] Excessive sweating was the most common side effect. Cevimeline, a similar agent with a more selective mechanism of action, was associated with a significant increase in unstimulated salivary flow at dosing of 30 to 45 mg three times a day.[232] Amifostine is a thiol with chemo- and radioprotectant properties. Objective and subjective measures of salivary function were improved in an open-label, randomized study among patients who received 200 mg/m^2 of amifostine intravenous daily 15 to 30 minutes before RT.[233] Grade 3 toxicities were infrequent, but nausea, vomiting, hypotension, and allergic reactions were more common among patients treated with amifostine. The benefits when given with chemoRT are more controversial.[234] There have been concerns regarding the potential of tumor protection by amifostine, but a recent meta-analysis did not demonstrate any adverse impact on progression-free or overall survival in patients treated with RT or chemoRT.[234] Finally, acupuncture may be of benefit in the management of xerostomia in selected patients.[38,235]

Mucositis is a troubling symptom typically exacerbated by aggressive altered fractionated RT programs and the use of concurrent chemoRT. A variety of rinses (e.g., topical anesthetics, antifungals) and systemic pain medications are used for symptomatic relief. Concurrent amifostine with RT has not been clearly shown to decrease mucositis.[233,234] Iseganan hydrochloride, a synthetic peptide with broad spectrum antibacterial activity, was evaluated in a multinational, double-blind, placebo-controlled trial among patients receiving definitive or postoperative RT-based therapy. No improvement in oral mucositis was found compared to placebo.[236] Recombinant human keratinocyte growth factor has been shown to decrease the incidence and duration of mucositis in the transplant setting.[237] Two randomized studies demonstrated improvement in observer-assessed mucositis with palifermin use, but no clear difference in patient-reported pain, opioid analgesic use, or treatment breaks when compared to placebo.[238,239]

FOLLOW-UP

How to optimally follow-up with patients after treatment for head and neck cancer is less well studied than how to treat it. Approaches are informed by patterns of failure. Most relapses occur within the first 3 years and are front loaded, and relapses above the clavicles are potentially curable. The lung is the most common site of distant spread.

The schedule proposed in the NCCN practice guidelines is reasonable.[146] Patients are seen for follow-up head and neck examinations every 1 to 3 months during year 1, every 2 to 6 months during

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year 2, every 4 to 8 months during years 3 to 5, and every 12 months thereafter. Thyroid function tests are obtained every 6 to 12 months if the neck was irradiated. Many practitioners obtain annual chest x-rays or other chest imaging to monitor for a second primary lung cancer and to document distant metastases. The impact of this imaging on outcomes is not well established, which is consistent with a vague recommendation from the NCCN of chest imaging "as clinically indicated." Tobacco history should be considered for purposes of lung cancer screening.[146] Posttreatment baseline imaging within 6 months of therapy is recommended. Additional studies such as CT, MRI, and PET scans may subsequently be necessary to determine whether there is a recurrence or a complication, but otherwise are not routinely performed in surveillance. Speech and swallowing evaluations and rehabilitation are obtained as indicated. Counseling is indicated for patients in whom tobacco or alcohol contributed as a risk factor for tumor development.

ORAL CAVITY

The oral cavity consists of the lips, the floor of mouth, the anterior two-thirds of the tongue, the buccal mucosa, the upper and lower alveolar ridges, the hard palate, and the retromolar trigone.

The AJCC staging system is used.[26]

LIP

The ratio between men and women with lip cancer is approximately 15:1.[240] Persons with light-colored skin and/or prolonged exposure to sunlight are most prone to develop lip carcinoma.

Anatomy

The lips are composed of the orbicularis oris muscle with skin on the external surface and mucous membrane on the internal surface. The transition from skin to mucous membrane is the lip vermilion. The blood supply is from the labial artery, a branch of the facial artery. The motor nerves are branches of cranial nerve (CN) VII. The sensory nerve to the upper lip is the infraorbital branch of CN V (V 2), and the mental nerve (V 3) supplies the lower lip.

Pathology

The most common neoplasms are SCCs. Basal cell carcinomas arise on the skin of the lip and may secondarily invade the vermilion. Keratoacanthoma occurs on the skin of the lips and may be mistaken grossly and histologically for SCC.

Leukoplakia and CIS are common problems on the lower lip and may precede the appearance of carcinoma by many years. Primary lesions arising from the moist mucosa of the lip are considered under the section *Buccal Mucosa*.

Patterns of Spread

SCC can originate from the skin of the lip or the vermilion, which may invade the adjacent skin and orbicularis muscle. Advanced lesions invade the adjacent commissures of the lip, the buccal mucosa, the skin and wet mucosa of the lip, the adjacent mandible, and eventually the mental nerve. PNI occurred in 2% of the cases reported by Byers and coworkers[241] and was related to recurrent lesions, large tumor size, mandibular invasion, and poorly differentiated histology. Lymphatic spread is to the submental (IA) and submandibular (IB) lymph nodes and then to the jugular chain. The risk for lymph node metastases is approximately 5% at diagnosis and is increased by high-grade histology, large lesions, invasion of the mucosa of the lip, and for patients with recurrent disease.

Clinical Picture

The vermilion of the lower lip is the most common site of origin. SCC may present as an enlarging discrete lesion that is not tender until it ulcerates. Some lesions develop slowly on a background of leukoplakia or CIS and present as superficially ulcerated lesions with little or no bulk. Erythema of the adjacent skin suggests dermal lymphatic invasion. Palpation of the lip will reveal the extent of induration. Paresthesia of the skin of the lip indicates PNI.

Treatment

Selection of Treatment Modality

Early lesions may be cured equally well with surgery or RT. Surgical excision is preferred for the majority of lower lip lesions up to 2 cm in diameter that do not involve the commissure; the treatment is simple and the cosmetic result is satisfactory. Removal of more of the lip with simple closure usually results in a poor cosmetic and functional result and, therefore, requires reconstructive procedures. RT is often preferred for lesions involving the commissure, for lesions over 2 cm in length, and for upper lip carcinomas. Advanced lesions with bone, nerve, or node involvement frequently require a combined modality approach.

The regional lymphatics are not treated electively for early cases. Advanced lesions, high-grade lesions, and recurrent lesions should be considered for elective neck treatment. Clinically positive nodes are managed as previously discussed in *Clinically Positive Neck Lymph Nodes*.

Surgical Treatment

Surgical treatment for early lesions (0.5 to 1.5 cm) utilizes a V- or W-shaped excision, depending on the size of the defect, which facilitates cosmetic primary closure. If the vermilion is diffusely involved with little or no involvement of the muscle, a vermilionectomy may be performed and the mucosa from the labial vestibule of the oral cavity advanced to cover the defect.

Irradiation Technique

Lip cancer may be successfully treated by EBRT, interstitial brachytherapy, or a combination of both. Interstitial brachytherapy may be accomplished with removable sources such as iridium-192 (^{192}Ir). EBRT techniques use orthovoltage (55.8 Gy at 1.8 Gy per fraction) or electrons (60 to 66 Gy at 2 Gy per fraction) with lead shields behind the lip to limit exit EBRT. IMRT is not indicated except for the occasional patient with advanced neck disease and/or clinical PNI where it is necessary to extend the dose distribution to the skull base and reduce the dose to the contralated parotid. For more advanced lesions, combining chemotherapy with EBRT is appropriately considered.[146]

Results of Treatment

MacKay and Sellers[242] reviewed 2,864 patients with all stages of lip cancer, of whom 92% were managed initially by RT. The primary lesion was controlled by the initial treatment in 84% of cases; an additional 8% were salvaged by later treatment for an overall local control rate of 92%. Of those who presented with clinically involved nodes, 58% had control of disease, but only 35% had control of disease when neck nodes appeared later. The 5-year, cause-specific survival rate was 89%; the 5-year absolute survival rate was 65%.

Mohs and Snow[243] reported the results for 1,448 patients treated with microscopically controlled surgery for SCCs of the lower lip between 1936 and 1976. Eighty-three percent had cancers less than 3 cm in diameter, with a 5-year cure rate of 96.6%. For 192 patients with cancers that measured 2 cm or more, the cure rate dropped to 60%.

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Complications of Treatment

Oral competence, which permits patients to control oral secretions and effectively suck, speak, and swallow, requires the sphincteric function of an intact orbicularis oris muscle. Hence, disruption of the sphincteric function resulting from division of the orbicularis oris should be restored. Microstomia and drooling secondary to oral incompetence may occur after a large flap reconstruction. If the oral opening is too small, the patient may not be able to inset a denture.

There will be some atrophy of the irradiated tissues; this progresses with time. Soft tissue necrosis may occur, but this problem is reduced by plans that prolong the treatment.

FLOOR OF THE MOUTH

Anatomy

The floor of the mouth is a U-shaped area bounded by the lower gum and the oral tongue; it terminates posteriorly at the anterior tonsillar pillar. The paired sublingual glands lie immediately below the mucous membrane; the paired genioglossus and geniohyoid muscles separate them. Bony protuberances, the genial tubercles, occur at the point of insertion of these two muscle groups at the symphysis. The mylohyoid muscle arises from the mylohyoid ridge of the mandible and is the muscular floor for the oral cavity; it ends posteriorly at about the level of the third molars. The submandibular gland rests on the external surface of the mylohyoid muscle between the mandible and the insertion of the mylohyoid. The submandibular duct (the Wharton duct) is about 5 cm long. It courses between the sublingual gland and the genioglossus muscle and exits in the anterior floor of the mouth near the midline.

Pathology

Most neoplasms are SCC, usually of moderate grade. Adenoid cystic and mucoepidermoid carcinomas account for about 5% of malignant tumors in this area.

Patterns of Spread

Primary

Approximately 90% of neoplasms originate within 2 cm of the anterior midline floor of the mouth, penetrating early beneath the mucosa into the sublingual gland and eventually into the genioglossus and geniohyoid muscles. The mylohyoid muscle acts as an effective barrier until the lesion becomes advanced. Extension toward the gingiva and periosteum of the mandible occurs early. When the tumor reaches the periosteum, the tumor usually spreads along the periosteum rather than through it. Mandible invasion is a late manifestation. The skin of the lower lip may be involved in advanced cases. Posterior extension occurs in the muscles of the root of the tongue. One or both submandibular ducts are frequently obstructed by the tumor or after the biopsy; it may be difficult to distinguish between tumor extension and infection in an obstructed duct. The submandibular gland frequently enlarges, becoming firm and occasionally painful when the duct is obstructed. Extensive lesions may follow the anatomic plane of the mylohyoid muscle to its posterior extremity and emerge in the submandibular space of the neck.

Lymphatic

Approximately 30% of patients will have clinically positive nodes on presentation; 4% will have bilateral nodes. The reported incidence of conversion from N0 to N+ with no neck treatment varies from 20% to 35%.[39,244] For T1 or superficial T2 lesions, the risk for occult metastasis is probably 10% to 15%.[39,244]

The first nodes involved are in levels IB and II; the risk for bilateral spread is fairly high.

Clinical Picture

On physical examination, the earliest lesions appear as a red area, slightly elevated, with ill-defined borders, and very little induration. As the lesion enlarges, the edges of the tumor become distinct, elevated, and "rolled," with a central ulceration and induration. Some lesions start with a background of leukoplakia. Bimanual palpation will determine the extent of the induration and the degree of fixation to the periosteum. Large lesions bulge into the submental space and rarely grow through the mylohyoid muscle into the soft tissues of the neck. Gross invasion of the mandible may be detected, especially when the anterior teeth have been removed. A tumor may grow through the mandible to involve the gingivolabial sulcus and lip. The submandibular duct and gland are evaluated by bimanual palpation.

Treatment

Selection of Treatment Modality

Early Lesions. Surgery or RT are equally effective treatments for T1 or T2 lesions. Most patients are treated surgically because of the risk of soft tissue or bone necrosis after RT.

A few patients are seen after excisional biopsy of a tiny lesion, and the only finding is a surgical scar with varying degrees of induration under the scar (TX). The margins are often equivocal. These patients are treated with reexcision or brachytherapy.

Moderately Advanced Lesions. The usual recommendation for moderately advanced anterior midline lesions is rim resection or segmental mandibulectomy and osteomyocutaneous free flap reconstruction; postoperative RT or chemoRT is added depending on the pathologic findings. The clinically N0 neck is usually managed by a bilateral functional neck dissection for midline lesions.

Advanced Lesions. Massive lesions have a poor prognosis with combined surgery and postoperative chemoRT. Only palliation can be offered in some cases.

Surgical Treatment

Wide Local Excision. Small lesions (5 mm or less in size) may be excised transorally with a 1-cm margin with primary closure or a skin graft. If the duct is involved, the submandibular gland and duct are removed in continuity.

Rim Resection. Rim resection of the mandible in continuity with excision of the primary lesion preserves the arch and may be combined with postoperative RT. Periosteal invasion is often an indication for this procedure. Patients who have been edentulous for a long time may have an atrophic mandible and are not suitable because the mandible is likely to fracture.

Segmental Mandibulectomy. A partial segmental mandibulectomy with resection of the floor of the mouth is done for lesions invading bone. An osteomyocutaneous flap is usually used to repair the defect.

Irradiation Technique

Superficial T1 cancers are treated with either brachytherapy or intraoral cone RT to approximately 65 Gy, and the neck is observed. Larger lesions are treated with EBRT to 45 to 50 Gy over 5 weeks followed by an interstitial implant for an additional 20 to 30 Gy. Lesions

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that are suitable for intraoral cone RT may be boosted with this technique prior to EBRT of the primary lesion and upper neck. Use of EBRT alone results in suboptimal cure rates and is discouraged.[245]

External-Beam Irradiation. Opposed lateral EBRT portals are used to treat anterior floor of the mouth carcinomas. The entire width of the mandibular arch is included and the superior border is shaped to spare part of the parotid gland. The level I and level II nodes are included to the level of the thyroid notch if the neck is clinically negative; the lower neck may be electively irradiated. If the neck is clinically positive, the portals are enlarged to include all of the upper neck nodes, and an en face low neck field is added. IMRT may be useful to reduce the dose to the contralateral parotid in patients with positive nodes.

Interstitial Irradiation. The implantation of T1 to T2 lesions confined to the floor of the mouth with minimal extension to the mucosa of the tongue can be accomplished with iridium using the plastic tube technique.

Intraoral Cone Irradiation. Intraoral orthovoltage or electron cone RT requires daily positioning by the physician and is preferable to interstitial RT because there is little or no irradiation of the mandible.[246] An intraoral cone can be used for well-circumscribed anterior superficial lesions and is easiest to perform in the edentulous patient.

Combined Treatment Policies

Postoperative RT is preferred, because the risk of bone complications and fistulae is higher with preoperative RT. Concurrent chemotherapy may be necessary based on pathologic findings.

Management of Recurrence

RT failures are treated by an operation. The salvage rate is good for patients with T1 to T2 lesions and poor for those with more advanced lesions.

Surgical treatment failures may be treated by a repeat operation and postoperative RT.

Results of Treatment

Rodgers et al.[247] reported on 194 patients treated with surgery and/or RT at the University of Florida between 1964 and 1987. The local control rates after RT versus surgery alone or combined with RT were: T1, 32 out of 37 (86%) versus 10 out of 11 (91%); T2, 25 out of 36 (69%) versus 16 out of 19 (84%); T3, 11 out of 20 (55%) versus 9 out of 9 (100%); and T4, 2 out of 5 (40%) versus 6 out of 10 (60%).[247] The 5-year cause-specific survival rates were comparable for the treatment groups.[247] Mild-to-moderate and severe complications were observed as follows: RT alone, 49 out of 117 (42%) and 6 out of 117 (5%); surgery alone, 3 out of 36 (8%) and 6 out of 36 (17%); and surgery and RT, 8 out of 41 (20%) and 6 out of 41 (15%), respectively.[247]

Two hundred seven patients treated with RT alone at the Centre Alexis Vautin between 1976 and 1992 were reviewed by Pernot and colleagues.[248] Local control and cause-specific survival rates at 5 years were as follows: T1, 97% and 88%; T2, 72% and 47%; and T3, 51% and 36%, respectively. Six percent of patients developed complications necessitating surgical intervention and one patient experienced a fatal complication.

Follow-Up

There are two major difficulties in follow-up after RT: soft tissue ulcers and enlarged submandibular glands. An ulcer in the floor of the mouth within 2 years of treatment can be either a recurrence or necrosis. If the lesion appears to be soft tissue necrosis, a trial of conservative therapy is adequate. Failure to stabilize or resolve is an indication for biopsy. A negative biopsy does not rule out recurrence, and repeat deep biopsies may be necessary. An enlarged submandibular gland(s) may be a sequel to obstruction of the submandibular duct; a contrast-enhanced CT is useful to distinguish between an enlarged submandibular gland and a tumor in a lymph node.

The follow-up for surgical cases may be difficult if skin grafts or flaps have been used because of the associated induration and thickness of the flaps. If the submandibular ducts have been reimplanted, stenosis may occur with subsequent enlargement of the submandibular glands.

Complications of Treatment

Radiation Therapy. A small soft-tissue necrosis may develop, usually in the site of the original lesion where the dose is highest. These are moderately painful and respond to local anesthetics, antibiotics, and the tincture of time. Treatment with pentoxifylline 400 mg three times daily may be beneficial.

If the ulceration develops on the adjacent gingiva, the underlying mandible is exposed. These areas are mildly painful. They are managed by discontinuing dentures, local anesthetics, antibiotics, and smoothing of the bone by filing, if needed. These small bone exposures do not often progress to osteoradionecrosis (ORN) and either sequestrate a small piece of bone or are simply recovered by the mucous membrane. Severe ORN may require daily hyperbaric oxygen (HBO) treatments for 4 to 6 weeks, either alone or in conjunction with surgical intervention.

Surgical. These include bone exposure, orocutaneous fistula, and failure of osteomyocutaneous flaps. Salvage procedures after RT are associated with an increased risk of complications.

ORAL TONGUE

Anatomy

The circumvallate papillae locate the division between the oral tongue and the base of the tongue. The arterial supply is mainly by way of paired lingual arteries that are branches of the external carotid. The sensory pathway is by way of the lingual nerve to the gasserian ganglion.

Pathology

More than 95% of oral tongue lesions are SCCs. Coexisting leukoplakia is common. Verrucous carcinoma and minor salivary gland tumors are uncommon. Granular cell myoblastoma is a benign tumor of uncertain origin that occurs on the dorsum of the tongue and may be confused histologically with carcinoma.

Patterns of Spread

Primary

Nearly all SCCs occur on the lateral and ventral middle and posterior thirds of the oral tongue. They tend to remain in the tongue until large unless they originate near the junction with the floor of the mouth. PNI and vascular space invasion may occur.

Anterior third lesions usually are diagnosed early. Advanced lesions invade the floor of the mouth and root of the tongue, producing ulceration and fixation. Posterior third lesions grow into the anterior tonsillar pillar and base of tongue.

Lymphatics

The first-echelon nodes are the level Ib and II nodes.[20] The submental and level V lymph nodes are seldom involved. Rouvière[13] describes lymphatic trunks that bypass the level I to II nodes and

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terminate in the level III lymph nodes. Byers et al.[249] evaluated nodal spread pattern in 277 patients treated surgically at the M.D. Anderson Cancer Center and observed skip metastases to the level III or IV nodes without involvement of levels I and II in 16% of patients. Of patients with oral tongue cancer, 35% have clinically positive nodes at diagnosis and 5% are bilateral. The incidence of occult disease is approximately 30%. The incidence of positive nodes increases with T stage. Patients with N1 or N2 ipsilateral nodes have a significant risk of developing node metastasis in the opposite neck.

Clinical Picture

Mild irritation of the tongue is the most frequent complaint. As ulceration develops, the pain worsens and is referred to the external ear canal. Extensive infiltration of the muscles of the tongue affects speech and deglutition and is associated with a foul odor.

The extent of disease is determined by visual examination and palpation. The tongue protrudes incompletely and toward the side of the lesion as fixation develops. Posterior oral tongue lesions may grow behind the mylohyoid and present as a mass in the neck at the angle of the mandible. Invasion of the hypoglossal nerve is rare.

Differential Diagnosis

The differential diagnosis includes granular cell myoblastomas, which are usually slow growing, nontender masses and 0.5 cm to 2.0 cm in size. The lesions are well circumscribed, firm, and slightly raised; they may be multiple. Aggressive behavior is rare, and wide local excision is preferred. Pyogenic granulomas mimic small exophytic carcinomas. Tuberculous ulcer and syphilitic chancre are rare.

Treatment

Selection of Treatment Modality

Both surgery and RT result in cure rates that are similar for similar stages. The disadvantages of surgery include removal of part of the tongue and the decision of whether to do a neck dissection for the N0 neck. The disadvantage of RT is the risk of necrosis.

Excisional Biopsy (TX). An excisional biopsy of a small lesion may show inadequate or equivocal margins. An interstitial implant or reexcision will produce a high rate of local control.

Early Lesions (T1 or T2). A partial glossectomy with primary closure or a skin graft may be done transorally and is usually the preferred therapy. Depending on the depth of invasion, an elective neck dissection may be indicated. Postoperative RT would only be added for indications previously discussed.

Moderately Advanced Lesions (T2 or T3). The preferred treatment for the majority of these patients is partial glossectomy, neck dissection, and postoperative RT-based treatment.

Advanced Lesions (T4). Bi- or trimodality treatment will cure a minority of these patients. Some patients are best treated with palliative intent.

Surgical Treatment

Early Lesions (T1 or T2). A partial glossectomy and primary closure is performed.

Moderately Advanced Lesions (T2 or T3). A partial glossectomy with primary closure, skin graft, or flap reconstruction is performed. Frozen section control is essential. Positive margins are an indication for excision of additional tissue.

Advanced Lesions (T4). Near total or total glossectomy and sometimes a laryngectomy is performed.

Irradiation Technique

The ability to control the primary lesion is enhanced by giving all or part of the treatment with an interstitial RT or by intraoral cone.[250–252] Superficial T1 tumors may be treated with ^{192}Ir brachytherapy alone using the plastic tube technique. Larger lesions that have an increased risk for subclinical neck disease may be treated with EBRT and a brachytherapy boost or with brachytherapy combined with an elective neck dissection. The time factor is critical for oral tongue cancer, and the EBRT part of the treatment is shortened (30 Gy in 10 once-daily fractions, or 38.4 Gy in 1.6 Gy twice-daily fractions) in order to increase the proportion of the RT given by either interstitial or intraoral cone therapy. The interstitial therapy is given after the EBRT; the intraoral cone therapy should be done prior to the EBRT. Elective neck RT is indicated for nearly all lesions.

Combined Treatment Policies

Postoperative RT or chemoRT is administered to the primary site and neck for indications previously outlined. IMRT may be useful to reduce the dose to one or both parotids.

Management of Recurrence

Local recurrence after RT or surgery is heralded by ulceration, pain, or increased induration. Recurrences have a slightly elevated or rolled border, whereas necroses do not. A biopsy should be done as soon as ulceration appears if it is within the original tumor site. Ulcers that appear on adjacent normal tissues are likely due to RT and not cancer.

RT failure is managed by surgery. Surgical failure occasionally is salvaged by re-resection and postoperative RT-based treatment. Recurrence in the soft tissues of the neck is rarely eradicated by any procedure.

Nodes appearing in a previously untreated neck are managed by neck dissection with or without postoperative RT or chemoRT.

Results of Treatment

The local control rates for 170 patients treated with RT alone versus surgery alone or with RT between 1964 and 1990 at the University of Florida included: for T1, 79% versus 76% ($p = 0.76$); for T2, 72% versus 76% ($p = 0.86$); for T3, 45% versus 82% ($p = 0.03$); and for T4, 0% versus 67% ($p = 0.08$).[253] The differences in 5-year survival between the two treatment groups were not statistically significant.

The results of brachytherapy alone or combined with EBRT for 448 patients treated at the Centre Alexis Vautin were reported by Pernot et al.[254] and revealed the following 5-year local control and survival rates: T1, 93% and 69%; T2, 65% and 41%; and T3, 49% and 25%, respectively. Shorter time intervals between brachytherapy and EBRT were associated with significantly improved local control and survival for those who received both modalities.

Complications of Treatment

Surgical. Orocutaneous fistula, flap necrosis, and dysphagia are the most common complications after surgery. Damage to the lingual nerve or the hypoglossal nerve is rare. Fistula and flap necrosis may result in carotid artery hemorrhage. Enunciation difficulties occur whenever the tongue is bound down by scarring. The incidence of complications increases for surgical salvage attempts after RT failure. Of 65 patients, 13 (20%) treated with surgery alone or combined with RT at the University of Florida developed significant complications.[253]

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Radiation Therapy. A minor soft-tissue necrosis is fairly common and is treated with broad-spectrum antibiotics, local anesthetics such as viscous lidocaine, and analgesics. Pentoxifylline 400 mg three times daily may be beneficial. Hyperbaric oxygen treatment may be tried in difficult cases. If the necrosis is persistent and the pain is uncontrollable, it must be resected.

The edentulous person is less likely to develop bone complications compared with those who are dentulous.[255] The most frequent problem involving the mandible is *bone exposure*. If the patient has dentures, they should be discontinued or altered to relieve the pressure over the exposed bone. If sharp bony edges appear, they are filed and the bone edge is lowered to speed healing. Healing may require months or even years.

If ORN develops, HBO has been used with some success. If conservative measures are unsuccessful, segmental mandibulectomy and an osteomyocutaneous flap reconstruction is performed.

Severe complications were observed in 9 of 105 patients (9%) treated with RT at the University of Florida.[253] Pernot and colleagues[254] observed the following soft tissue and/or bone complications in a series of 448 patients: Grade 1, 19%; Grade 2, 6%; and Grade 3, 3%.

BUCCAL MUCOSA

Epidemiology

SCC is relatively uncommon in the United States. In Southern India, it is common and is related to chewing a combination of tobacco mixed with betel leaves, areca nut, and lime shell.[256]

Anatomy

The buccal mucosa is the mucous membrane covering the inner surface of the cheeks and lips, ending above and below with a transition to the gingiva. It ends posteriorly at the retromolar trigone. The parotid duct opens into the buccal mucosa opposite the second upper molar. The buccal mucosa is innervated by a branch of the mandibular nerve.

Pathology

Most malignant tumors are low-grade SCCs that frequently appear on a background of leukoplakia or lichen planus. Verrucous carcinoma occurs. Minor salivary gland tumors and melanomas are rare.

Patterns of Spread

Early lesions are usually discrete and exophytic. As they enlarge, they penetrate the underlying muscles and eventually extend to the skin. Peripheral growth occurs into the gingivobuccal sulci and eventually onto the gingiva and into bone.

The lymphatic spread is first to the level I and level II nodes. The incidence of positive nodes on admission is 9% to 31%, and the risk of occult disease is 16%.[20,244]

Clinical Picture

Small lesions produce the sensation of a lump that is felt with the tongue. Pain is minimal, unless there is posterior extension to involve the lingual and dental nerves. Pain may be referred to the ear. Obstruction of the Stensen duct will produce parotid enlargement. Extension posteriorly, behind the pterygomandibular raphe or into the buccinator and masseter muscles, causes trismus.

Differential Diagnosis

The differential diagnosis includes lues and tuberculosis; both are rare. If the first biopsy reveals chronic inflammation or pseudoepitheliomatous hyperplasia, a repeat biopsy may be necessary.

Treatment

Selection of Treatment Modality

Small lesions (≤1 cm) may be excised with primary closure; small lesions that involve the lip commissure are sometimes treated by RT. Lesions 2 cm to 3 cm in size can be treated with surgery or by RT (usually the former). Larger lesions are usually treated with surgery, and postoperative RT or chemoRT.

Surgical Treatment. Lesions that invade the mandible or maxilla require bone resection along with the soft tissues. Repair may require a maxillary prosthesis. A myocutaneous flap repairs full-thickness removal of the cheek.

Irradiation Technique. Buccal mucosa lesions are suited for treatment with electrons, an intraoral cone, and interstitial techniques to spare the contralateral normal tissues. When tumors extend into one of the gingivobuccal gutters or onto bone, treatment must be entirely by EBRT.

Results of Treatment

Diaz et al.[257] recently reported the M.D. Anderson experience for 119 patients treated with surgery alone (84 patients) or combined with adjuvant RT (35 patients) between 1974 and 1993. Tumor recurrence developed in 54 patients (45%): local recurrence in 27 patients (23%); regional recurrence in 13 patients (11%); local and regional recurrence in 11 patients (9%); and distant metastases in 3 patients (3%). The 5-year survival rates versus stage were stage I, 78%; stage II, 66%; stage III, 62%; stage IV, 50%; and overall, 63%.

Nair and coworkers[256] reported the definitive RT results for 234 cases of buccal mucosa cancer treated in southern India during the 1982 calendar year. The 3-year disease-free survival rates were stage I, 85%; stage II, 63%; stage III, 41%; and stage IV, 15%. Thirty-two patients had verrucous carcinoma, and the 3-year disease-free survival rate was 47%, similar to that for other grades of SCC.

Complications of Treatment

The buccal mucosa is tolerant of high-dose RT, and complications are uncommon. Bone exposure may appear on the mandible or maxilla. Trismus may develop if the muscles of mastication receive high doses.

Surgical injury of the Stensen duct may cause obstruction and parotitis. Injury to branches of the VII nerve may occur. Split-thickness skin grafts may shrink and produce a partial trismus. Resection of the lip commissure may produce oral incompetence.

GINGIVA AND HARD PALATE (INCLUDING RETROMOLAR TRIGONE)

Anatomy

The lower gingiva includes the keratinized masticatory mucosa covering the mandible from the gingivobuccal gutter to the origin of the nonkeratinized lining mucosa covering the floor of the mouth. The retromolar trigone lies behind the third molar and is contiguous superiorly with the maxillary tuberosity. Beneath the keratinized mucosa of the retromolar trigone is the tendinous pterygomandibular raphe, which is attached to the pterygoid hamulus and the posterior mylohyoid ridge of the mandible and serves

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as the insertion of the buccinator, orbicular oris, and superior pharyngeal constrictor muscles. Behind the pterygomandibular raphe and between the medial pterygoid muscle and the ascending ramus is the pterygomandibular space, which contains the lingual and dental nerves and is related posteriorly to the deep lobe of the parotid and the parapharyngeal space. There are no minor salivary glands in the mucous membranes of the alveolar ridges.

Pathology

Most neoplasms are SCCs. Minor salivary gland tumors, usually adenoid cystic carcinomas, often occur on the posterolateral hard palate.[258] Verrucous carcinomas usually occur on the lower gingiva. Melanoma has been reported.[259]

SCC may arise within the body of the mandible or maxilla either from the odontogenic epithelium or from epithelium trapped during embryonic development. It is more frequent in the mandible than the maxilla and is most common in the molar regions. It must be distinguished from metastatic SCC and ameloblastoma.

Ameloblastoma is a rare, benign locally aggressive odontogenic tumor with an incidence of about 1% of all tumors of the maxilla and mandible; about 80% of cases occur in the mandible with the molar–ramus region most commonly involved.

Patterns of Spread

Lower Gum

SCC invades the periosteum and the adjacent buccal mucosa and floor of the mouth. Low-grade lesions tend to produce a smooth, saucerized defect before invading the mandible. Moderate to high-grade lesions invade the bone directly or through recently opened dental sockets and produce a lytic defect.

Lymphatic spread is to the level I and level II nodes. Clinically positive nodes occur in 18% to 52% of diagnoses; occult disease occurs in 17% to 19%.[20,244]

Ameloblastoma expands and destroys the bone and extends to adjacent areas by contiguous growth. Ameloblastic carcinoma, a rare malignant variant of ameloblastoma, may metastasize to regional nodes and distant sites.[260]

Upper Alveolar Ridge and Hard Palate

Most SCCs originate on the gingiva and spread secondarily to the hard palate, soft palate, buccal mucosa, and underlying bone. The maxillary antrum is invaded late unless there are recent extractions providing access. The risk for positive lymph nodes at diagnosis is 13% to 24%, and the incidence of occult disease is 22%.[20,244]

Retromolar Trigone

Carcinomas spread to the adjacent buccal mucosa, the anterior tonsillar pillar, and the maxilla. Posterior spread occurs into the pterygomandibular space and the medial pterygoid muscle. Posterolateral spread occurs into the buccinator muscle and fat pad. The first echelon lymphatics are the level I and level II nodes. The incidence of clinically positive nodes on presentation is about 30%; the risk for occult disease is 15% to 25%.

Clinical Picture

The patient with SCC may present to the dentist first with ill-fitting dentures, pain, loose teeth, or a sore that will not heal. A history of inappropriate dental extractions or root canal therapy is common. Invasion into the mandible may involve the inferior alveolar nerve and produce paresthesia of the lower lip. A background of leukoplakia is frequently present.

Retromolar trigone lesions have pain referred to the external auditory canal and preauricular area. Invasion of the pterygoid muscle produces trismus. Intra-alveolar SCC presents with a submucosal mass and dental symptoms. Roentgenograms show a lytic lesion in the mandible.

Ameloblastoma exhibits few symptoms in the early stages. Patients may notice a gradually increasing facial deformity or a loosening of teeth. An intraoral submucosal mass may be present initially; ulceration occurs as the mass increases in size. On roentgenograms, a radiolucent area is seen with the expansion of the overlying cortical plate, scalloped margins, a multilocular appearance, and/or resorption of the roots of adjacent teeth.

Minor salivary gland tumors present as a submucosal mass, enlarge slowly, and may develop a central ulceration.[261]

Differential Diagnosis

The differential diagnosis includes dental disease and underlying bony cysts or tumors.

Treatment

Selection of Treatment Modality

Lower Alveolar Ridge. The majority of lesions are managed by surgery alone or followed by postoperative RT or chemoRT. Surgery entails a marginal mandibulectomy when there is, at most, saucerization of the underlying bone. Segmental mandibulectomy and free flap reconstruction is indicated for more advanced disease.

Ameloblastoma. The treatment is surgery; however, local recurrence is a problem. Sehdev and coworkers[262] reported curettage was followed by local recurrence in 90% of mandibular ameloblastomas and in all maxillary ameloblastomas. Subsequent resection controlled 80% of the mandibular but only 40% of the maxillary tumors. The initial use of segmental mandibular resection controlled 78% (18 of 23 patients), with subsequent resection controlling those that recurred. The use of partial maxillectomy as the first treatment controlled 100% (7 of 7 patients) of maxillary ameloblastomas as opposed to only 40% when a partial maxillectomy was performed for recurrence. Limited experience with RT suggests that it may reduce the probability of progression and result in long-term local control in the occasional patient with incompletely resectable disease.[260]

Retromolar Trigone. Surgery is preferred for discrete early lesions. RT is recommended for superficial lesions involving a large surface area.[263] Advanced carcinomas are treated with surgery and postoperative RT or chemoRT

Upper Alveolar Ridge and Hard Palate. Resection alone or followed by RT or chemoRT is the usual treatment for most lesions. However, if the lesion is superficial and extensively involves the hard palate or involves a significant portion of the soft palate, then an RT-based approach should be considered for the initial therapy. If the lesion is small and discrete and there is no bone involvement, resection includes the periosteum or occasionally some underlying bone. Bone invasion requires a maxillectomy that is tailored to optimally resect the cancer. The resulting defect is usually rehabilitated with a removable prosthesis.

Irradiation Technique

Small lesions of the lower alveolar ridge and retromolar trigone may be treated by intraoral cone for all or part of their therapy. Well-lateralized lesions of the retromolar trigone and posterior alveolar ridge may be treated by either an ipsilateral mixed beam or IMRT; the latter is preferred. Parallel-opposed portals treat anterior gum lesions.

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Carcinomas that involve a large surface area with little or no bone invasion may be treated by EBRT. T1 to T2 carcinomas are treated with altered fractionation; larger tumors are treated with chemoRT.

Management of Recurrence

RT failures are managed by operation. Surgical failures may be managed by surgery and postoperative RT or chemoRT[264]; Salvage procedures frequently are not attempted because of the advanced nature of the recurrence and the low chance of cure.

Results of Treatment

Mandibular Gingiva. Overholt and coworkers[265] reported 155 patients with SCCs of the lower alveolar ridge treated at M.D. Anderson between 1970 and 1990. Surgery alone was used for 131 patients; the remainder received surgery and RT. Five-year survival for patients with T1 and T2 cancers were 85% and 84%, respectively, compared with 66% and 64%, respectively, for those with T3 and T4 malignancies. Local control at 2 years was impacted by tumor size ($p = 0.021$) and margin status ($p = 0.027$), whereas 5-year cause-specific survival was influenced by tumor size ($p = 0.001$), margin status ($p = 0.011$), mandibular invasion ($p \leq 0.05$), and the presence of lymph node metastases ($p < 0.001$).

Retromolar Trigone. Byers and coworkers[266] reported the M.D. Anderson results for 110 previously untreated patients with SCC of the retromolar trigone treated between 1965 and 1977, with a minimum 5-year follow-up. Surgery was often selected for patients with leukoplakia, poor teeth, mandible invasion, large neck nodes, or trismus. RT was selected for poorly differentiated tumors, for mainly exophytic lesions, and lesions involving the faucial arch or soft palate or lesions having ill-defined borders, and for poor surgical risk cases. The local control rates were as follows: T1, 12 of 13 (92%); T2, 50 of 57 (88%); T3, 18 of 20 (90%); and T4, 15 of 20 (75%). Local control was similar after surgery and/or RT. The absolute 5-year survival rate was 26%.

Mendenhall and coworkers[263] reported on 99 patients with retromolar trigone SCCs treated between 1966 and 2003 with RT alone (35 patients) or combined with surgery (64 patients). The 5-year local–regional control rates after RT versus surgery and RT were for stages I through III, 51% and 87%; for stage IV, 42% and 62%; and overall, 48% and 71%, respectively. The 5-year cause-specific survival rates after RT versus surgery and RT were for stages I through III, 56% and 83%; for stage IV, 50% and 61%; and overall, 52% and 69%, respectively. A multivariate analysis revealed that the likelihood of cure was better after surgery and RT compared with definitive RT.

Hard Palate. Shibuya and coworkers[267] reported the results for 38 cases of carcinoma of the hard palate and 82 cases of carcinoma of the upper alveolar ridge treated between 1953 and 1982 in Japan. Sixty-six patients were managed initially by RT alone to the primary lesion, and 54 patients were managed by RT and surgery. The 5-year actuarial survival rate by stage was the following: for stage I, 56%; for stage II, 41%; for stage III, 32%; and for stage IV, 12%. There was no difference in survival when comparing hard palate versus upper alveolar ridge, SCC versus minor salivary gland tumors, or RT alone versus RT plus surgery as the initial therapy. The overall risk for metastatic lymph nodes was 47% for hard palate and 49% for the upper alveolar ridge. Thirty patients were recorded as having "slight bone invasion," and no metastases had a 5-year survival rate of 75% when treated by RT.

Complications of Treatment

Surgical complications include orocutaneous fistula, bone exposure, extrusion of a metal tray, and loss of graft or flap.

The complications of RT include soft tissue necrosis, bone exposure, and ORN. The risk is greatest for patients with advanced lesions of the lower gum and retromolar trigone. Huang and colleagues[268] reported the following rates of grade 3 bone and soft tissue complications in 65 patients treated for retromolar trigone carcinomas: preoperative RT, 0 of 10 patients (0%); surgery and postoperative RT, 5 of 39 patients (13%); and RT alone, 2 of 16 patients (13%).

OROPHARYNX

ANATOMY

The base of the tongue is bounded anteriorly by the circumvallate papillae, laterally by the glossotonsillar sulci, and posteriorly by the epiglottis. The vallecula is a strip of mucosa that is the transition from the base of the tongue to the epiglottis; it is considered part of the base of tongue. The musculature of the base of the tongue is contiguous with that of the oral tongue.

The tonsillar fossa is bounded anteriorly by the anterior tonsillar pillar (palatopharyngeal muscle), posteriorly by the posterior tonsillar pillar (palatopharyngeal muscle), and inferiorly by the glossotonsillar sulcus and pharyngoepiglottic fold. The pharyngeal constrictor muscle and its fascia, the mandible, and the lateral pharyngeal space bound the tonsillar region laterally. The tonsillar area is separated from the base of tongue by the glossotonsillar sulcus, which extends from the anterior tonsillar pillar to the pharyngoepiglottic fold. Beneath the mucous membrane of the sulcus are the styloglossal muscle and the stylohyoid ligament.

The soft palate is a thin, mobile muscle complex separating the nasopharynx from the oropharynx. The epithelium of the oral side of the soft palate is squamous; the epithelium of the nasopharyngeal surface is respiratory. It is contiguous laterally with the tonsillar pillars.

PATHOLOGY

SCC accounts for 95% of cancers. Lymphoepitheliomas occur in the tonsillar fossa and the base of tongue. Basaloid features suggest a HR-HPV related tumor. Lymphomas account for 5% of tonsillar and 1% to 2% of base of tongue malignancies. Minor salivary gland malignancies, plasmacytomas, and other rare tumors make up the remainder.[269,270]

PATTERNS OF SPREAD

Base of Tongue

Primary

Base of tongue SCC usually remains in the tongue unless it begins at the peripheral margin. Lateral base of tongue cancers may invade the glossotonsillar sulcus and eventually escape into the neck, because there is no effective musculature barrier at this point. Vallecular lesions spread along the mucosa to the lingual surface of the epiglottis, laterally along the pharyngoepiglottic fold, and then to the lateral pharyngeal wall and anterior wall of the pyriform sinus. Vallecular lesions frequently penetrate through the hyoepiglottic ligament to enter the preepiglottic space.

Lymphatic

The first-echelon nodes are in level II; spread is then to the level III and level IV nodes. The level Ib nodes are at risk if the tumor extends into the oral tongue or if massive upper neck disease is present. The level V nodes are involved often enough to be included

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in treatment plans. Approximately 75% of patients will have clinically positive neck nodes at diagnosis, and 30% will have bilateral nodes.[20] The risk of occult disease in the clinically negative neck is probably 40% to 50%.

Tonsillar Area

Anterior Tonsillar Pillar

Almost all malignancies are SCCs, and they tend to be diagnosed early when they are relatively superficial with indistinct borders. As the lesions progress, they may develop a central ulcer with a rolled margin and infiltrate the palatoglossus. The lesion may extend superiorly onto the soft palate and posterior hard palate, anterolaterally to the retromolar trigone and buccal mucosa, and inferomedially into the tongue. As these lesions advance, they eventually invade bone, extend to the skull base and nasopharynx, and invade the medial pterygoid muscle, causing trismus and temporal pain.

Tonsillar Fossa

The initial lesions tend to be exophytic with central ulceration plus an infiltrative component. As the tumor progresses, it extends into the posterior tonsillar pillar, the oropharyngeal wall, and the base of tongue. It eventually penetrates the parapharyngeal space and grows superiorly to the skull base.

Posterior Tonsillar Pillar

Posterior tonsillar pillar lesions may spread inferiorly along the palatopharyngeal muscle to its insertions into the middle pharyngeal constrictor, the pharyngoepiglottic fold, and the posterior border of the thyroid cartilage.

Lymphatic

Retromolar trigone/anterior tonsillar pillar lesions have a lower risk of clinically positive lymph nodes (45%) compared with the tonsillar fossa (76%). The distribution for the retromolar trigone/anterior tonsillar pillar on the ipsilateral side is to the jugular and level IB lymph nodes with a low risk for junctional and level V nodes. Contralateral spread is uncommon (5%) and is confined to the jugular chain. The risk of occult disease in the clinically negative neck (N0) is 10% to 15%. The incidence of positive nodes increases with T stage.

The lymph node distribution for tonsillar fossa lesions on the ipsilateral side includes the jugular, junctional, level V, and level IB lymph nodes. Contralateral spread occurs in 11% of patients and is mainly to the jugular chain lymph nodes. The risk of contralateral spread is related to invasion of the tongue near the midline of the soft palate and large ipsilateral lymph nodes that produce lymphatic obstruction. The incidence of occult disease is probably 50% to 60%.

Soft Palate

Primary

Nearly all SCCs occur on the oral side of the palate. The earliest tumors are red lesions with ill-defined borders. Spread occurs first to the tonsillar pillars and hard palate. Lateral spread may eventually penetrate the superior constrictor muscle and skull base and invade the lateral wall(s) of the nasopharynx.

Lymphatic

The spread pattern is first to the level II nodes and then to levels III and IV. Approximately 56% of patients have clinically positive nodes at presentation; 16% are bilateral.[20] The incidence of occult neck disease is approximately 20%.[271] The incidence of clinically positive nodes increases with T stage.[20]

CLINICAL PICTURE

Base of Tongue

Often, the earliest symptom is a mild sore throat or a level II neck mass. Difficulty swallowing, a nasal voice quality, and ear pain occur as the lesion enlarges. Advanced lesions fix the tongue.

Flexible fiber optic endoscopy and digital palpation are necessary for the diagnosis of early lesions of the base of tongue.

Lymphomas are usually large, mostly submucosal masses. Minor salivary gland tumors are also usually submucosal, but more discrete and firm than lymphomas.

Tonsillar Area

Anterior Tonsillar Pillar

Early symptoms include sore throat, and pain is referred to the ear. As the lesion progresses, it may cause trismus and temporal pain.

Tonsillar Fossa

An ipsilateral sore throat is common. Detection by visual examination with a tongue depressor is sufficient for most lesions. Some patients present with a node in the neck. Lymphomas tend to be large submucosal masses, but may ulcerate and appear similar to carcinomas.

Soft Palate

Patients may present with a mild sore throat that is not well localized. Advanced lesions may cause swallowing dysfunction, voice changes, regurgitation of food into the nasopharynx, trismus, temporal pain, and, rarely, CN involvement.

STAGING

The AJCC staging system is used.[26] Invasion of the deep musculature of the tongue is diagnosed if the tongue is partially fixed. Lesions that produce trismus or CN palsy are classified as T4. Pathologic staging usually results in "upstaging." Stage migration renders a meaningful comparison of outcomes between clinically and pathologically staged patients nearly impossible.

TREATMENT: BASE OF TONGUE

Selection of Treatment Modality

Surgery and RT produce similar cure rates. Because excision of the base of tongue generally causes greater disability and because of the high risk for bilateral lymphatic involvement, RT or chemoRT is usually the treatment of choice.[272]

Surgical Treatment

Patients with a low-volume T1 or early T2 cancer may be suitable for transoral laser excision and a neck dissection.[273] Transoral robotic surgery is increasingly used to facilitate resection with less morbidity. Otherwise, the surgical approach requires an incision, which splits the lip, and a mandibulotomy, which permits lateral rotation of the mandible. Suprahyoid, transhyoid, and infrahyoid approaches also can be used to resect small lesions. After the tumor has been removed, the mandibular edges are reapproximated and stabilized with a titanium reconstruction plate. Only one lingual artery may be sacrificed. A neck dissection is done

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in continuity with excision of the primary lesion. Removal of a large tumor requires the simultaneous removal of part of or the entire larynx.

Irradiation Technique

Parallel opposed EBRT portals encompass the primary site and bilateral cervical nodes. Interstitial brachytherapy with flexible sources, such as ^{192}Ir ribbons, may be used for part of the treatment if the lesion is relatively limited. In contrast to oral tongue cancer, there is no proven advantage in local control for interstitial boosts compared with EBRT alone.

One of the common errors in planning EBRT is a failure to recognize anterior tumor extension into the lateral floor of the mouth; this is usually appreciated on CT and/or MRI. The inferior border of the lateral portals is usually the thyroid notch unless the tumor has extended into the upper pyriform sinus or preepiglottic space.

The primary portals include the level I_B, II, and V nodes when the neck is N0. The superior border is approximately 2 cm above the tip of the mastoid even with clinically negative nodes to ensure coverage of the nodes near the skull base.

The bilateral lower neck nodes are always treated with a separate anterior portal. If the upper neck is clinically negative, the lower neck portals include the level 3 and 4 nodes. If the upper neck is clinically positive, the lower neck portals are more generous.

Patients are treated with 1.2 Gy per fraction twice daily to 74.4 to 76.8 Gy. An alternative is 70 Gy in 35 fractions over 30 treatment days using simultaneous integrated boost (SIB) and a concomitant boost. Most patients with a N0 neck or ipsilateral positive nodes are treated with IMRT to reduce the dose to the contralateral parotid.

Management of Recurrence

RT treatment failures are treated surgically; salvage is infrequent except for T1 and early T2 lesions. Surgical treatment failures are rarely salvaged, except for the early lesion with a discrete local recurrence. Palliative management is often preferred.

RESULTS OF TREATMENT: BASE OF TONGUE

The 5-year local control rates after definitive RT in a series of 333 patients treated at the University of Florida were for T1, 98% (n = 46); for T2, 92% (n = 125); for T3, 82% (n = 92); and for T4, 53% (n = 70).[272] The 5-year local–regional control, distant metastasis-free survival, and survival rates are depicted in Table 38.11. Severe, acute, late, and/or postoperative complications developed in 52 patients (16%).

FOLLOW-UP: BASE OF TONGUE

RT failures may present as an ulcer and must be distinguished from necrosis. Deep biopsies usually must be done under general anesthesia to obtain adequate tissue and control bleeding.

COMPLICATIONS OF TREATMENT: BASE OF TONGUE

Surgical Complications

These include an operative mortality of about 5%. Other complications include fistula, mandibular necrosis, dysphagia, aspiration pneumonia, hoarseness, trismus, and carotid rupture.

Complications of Irradiation

Bone exposure and ORN are uncommon. Mild-to-moderate soft tissue necroses occur in approximately 10% of patients, and mild-to-moderate bone exposures occur in 5% of patients treated solely by EBRT. Necroses may persist for several months and may respond to pentoxifylline. Hypoglossal nerve palsy occurs rarely.

Occasionally, patients may have difficulty swallowing due to fibrosis of the base of the tongue compounded by xerostomia. Significant aspiration is unusual. It is uncommon for a patient to develop severe swallowing disability requiring a PEG.[274]

TREATMENT: TONSILLAR AREA

Selection of Treatment Modality

The cure rates are similar after definitive RT-based treatment compared with surgery alone or combined with adjuvant RT.[275] Because morbidity is generally higher after surgery, definitive RT or chemoRT is often preferred.

Surgical Treatment

Surgery for early cancers consists of a transoral wide local excision. Transoral robotic surgery is increasingly used for surgical procedures of this site to facilitate resection with less morbidity. Larger lesions may require removal of the adjacent mandible as well as a portion of the tongue and soft palate. Depending on the size of the defect, a tongue, deltopectoral, or osteomyocutaneous flap may be required. Speech may be impaired if a significant portion of the tongue or palate has been removed.

TABLE 38.11

Base of Tongue: 5-Year Outcomes After Radiotherapy at the University of Florida (333 Patients)

Stage	No. of Patients	Local–Regional Control	Ultimate Local–Regional Control	Distant Metastasis-Free Survival	Cause-Specific Survival	Survival
I–II	26	100%	100%	92%	91%	67%
III	58	82%	87%	90%	77%	66%
IVA	124	87%	90%	92%	84%	67%
IVB	125	58%	62%	69%	45%	33%

From Mendenhall WM, Morris CG, Amdur RJ, et al. Definitive radiotherapy for squamous cell carcinoma of the base of tongue. *Am J Clin Oncol* 2006;29:32–39.

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Irradiation Technique

The portal arrangement depends on the extent of local–regional disease. If the risk for contralateral lymph node metastases is low, an ipsilateral IMRT technique is employed to reduce xerostomia.

More advanced lesions are treated with parallel opposed photon portals, usually weighted 2 to 1 or 3 to 2 to the involved side. If there are positive contralateral nodes or extension across the midline, the portals usually are equally weighted. The inferior border is placed 2 cm below the primary tumor. IMRT may be employed to irradiate both sides of the neck and reduce the dose to the contralateral parotid in patients with a N0 neck or ipsilateral positive neck nodes. The low neck is treated with a separate anterior field with a thin midline block over the larynx. Small, discrete lesions of the anterior tonsillar pillar may have part of the RT by intraoral cone.

The dose for tonsillar lesions is 74.4 to 76.8 Gy (1.2 Gy twice daily) for T1 to T3 lesions, and 76.8 Gy for T4 lesions. An alternative is 70 Gy in 35 fractions over 30 treatment days using SIB and concomitant boost.

Management of Recurrence

Surgery will salvage a good portion of T1 or T2 RT failures, but only an occasional advanced lesion is salvaged.

RESULTS OF TREATMENT: TONSILLAR AREA

The 5-year local control rates after definitive RT in a series of 503 patients treated at the University of Florida between 1964 and 2003 for cancer of the anterior tonsillar pillar versus tonsillar fossa/posterior tonsillar pillar were for T1, 70% versus 94%; for T2, 74% versus 90%; for T3, 72% versus 79%; and for T4, 57% versus 62%.[275] The local control rates are better for tonsillar fossa/posterior tonsillar pillar cancers compared with those arising in the anterior tonsillar pillar. The 5-year local–regional control, distant metastases-free survival, and survival rates are depicted in Table 38.12.[275]

COMPLICATIONS OF TREATMENT: TONSILLAR AREA

Radiation Therapy

The risk for a severe complication, usually a bone or soft tissue necrosis, requiring surgical intervention is low. The probability of a fatal complication is remote. An occasional patient, usually one treated for advanced disease, may have long-term swallowing problems. Other complications include trismus, hypoglossal nerve entrapment, and a remote risk of an RT-induced malignancy and/or myelitis. Severe late complications occurred in 46 of 503 patients (9%).[275]

SURGICAL TREATMENT

Complications of operation include impaired swallowing, fistula, flap failure, poor wound healing, and aspiration occasionally leading to laryngectomy. The risk of severe and/or fatal complications is higher after surgery compared with RT.[275]

TREATMENT: SOFT PALATE

Selection of Treatment Modality

Although small, well-defined lesions may be excised and the neck observed, the risk of subclinical regional disease is high. Therefore, definitive RT is indicated for nearly all soft palate carcinomas; neck dissection is added as needed. Concomitant chemotherapy is indicated for patients with T3 to T4 and/or N2 to N3 disease.

Surgical Treatment

Small, discrete lesions can be managed by transoral excision and repaired by a pharyngeal flap to prevent any velopharyngeal incompetence. A tonsillectomy may also be necessary in order to obtain an adequate margin. If full-thickness resection is performed, a prosthesis is often required.

Irradiation Technique

The RT technique involves equally weighted, parallel opposed EBRT portals that include the primary lesion and the bilateral first-echelon upper neck nodes. A separate anterior portal is used to treat the low neck. If the primary lesion is discrete and the neck is clinically negative, a portion of the treatment may be given with an intraoral cone prior to EBRT.

Patients are treated with 4 to 6 MV photons to 74.4 to 76.8 Gy at 1.2 Gy per fraction, twice daily, in a continuous course. Another option is 70 Gy in 35 fractions over 30 treatment days. IMRT using the concomitant boost technique may be used to reduce the dose to one or both parotids.

Management of Recurrence

A persistent ulcer after RT is indicative of recurrent disease. Patients with a limited local recurrence after RT for a T1 or T2 lesion may be suitable for surgical salvage.

TABLE 38.12

Tonsillar Region: 5-Year Outcomes After Definitive Radiotherapy at the University of Florida (503 Patients)

Stage	No. of Patients	Local–Regional Control	Ultimate Local–Regional Control	Distant Metastasis-Free Survival	Cause-Specific Survival	Survival
I	22	66%	92%	100%	100%	54%
II	83	75%	88%	95%	86%	61%
III	95	85%	88%	97%	84%	62%
IVA	184	76%	84%	85%	73%	57%
IVB	119	58%	66%	68%	46%	33%

From Mendenhall WM, Morris CG, Amdur RJ, et al. Definitive radiotherapy for tonsillar squamous cell carcinoma. *Am J Clin Oncol* 2006;29:290–297.

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RESULTS OF TREATMENT: SOFT PALATE

Chera and coworkers[276] reported on 145 patients treated with definitive RT at the University of Florida between 1963 and 2004. Local control rates at 5 years were for T1, 90%; for T2, 90%; for T3, 67%; for T4, 57%; and overall, 81%. The 5-year local–regional control and cause-specific survival rates were for stage I, 84% and 89%; for stage II, 85% and 87%; for stage III, 66% and 88%; for stage IVA, 59% and 57%; and for stage IVB, 43% and 0%, respectively.[276]

COMPLICATIONS OF TREATMENT: SOFT PALATE

Surgical Complications

Nasal speech and regurgitation of food into the nasopharynx are sequelae of full-thickness soft palate resection. A prosthesis is partially successful in correcting the functional deficit.

Complications of Irradiation

Soft-tissue necrosis is uncommon. The soft palate may become retracted following successful treatment of advanced lesions and may result in regurgitation into the nasopharynx and a slight alteration in speech. ORN requiring surgical management is rare. Severe late complications were observed in 8 of 145 patients (6%) treated with definitive RT.[276]

LARYNX

Cancer of the larynx is primarily related to cigarette smoking.[277] The effect of alcohol remains unclear, but it is probably less impactful for the larynx than for the other head and neck sites.[277]

ANATOMY

The larynx is divided anatomically into the supraglottis, glottis, and subglottis. The supraglottis consists of the epiglottis, false vocal cords, ventricles, aryepiglottic folds, and arytenoids; the arytenoids are cartilages that articulate on the cricoid. The glottis includes the true vocal cords and the anterior commissure. The subglottis is 2 cm long and extends from 5 mm below the free edge of the true vocal cords to the lower margin of cricoid cartilage.

The preepiglottic space is bounded by the epiglottis posteriorly, the hyoepiglottic ligament and vallecula superiorly, and the thyroid cartilage and thyrohyoid membrane anteriorly and laterally. It can be seen as a low-density area on a CT scan.

The supraglottis has a moderately rich capillary lymphatic plexus. The lymphatic trunks pass through the preepiglottic space and the thyrohyoid membrane to the level II nodes. A few trunks drain directly to the level III or level IV nodes. There are essentially no capillary lymphatics of the true vocal cords. The subglottis area has relatively few capillary lymphatics. The lymphatic trunks pass through the thyrocricoid membrane to the midline pretracheal (Delphian) node(s) in the region of the thyroid isthmus and/or to the level IV nodes. The subglottis also drains posteriorly through the cricotracheal membrane with some trunks going to the paratracheal (level VI) nodes, whereas others pass to the level IV nodes.

PATHOLOGY

Nearly all laryngeal cancers arise from the surface epithelium and are SCCs. Minor salivary gland tumors are rare; even rarer are soft-tissue sarcomas, lymphomas, neuroendocrine carcinomas, and plasmacytomas. Hemangiomas, chondromas, and osteochondromas are reported, but their malignant counterparts are rare.

Distinguishing between CIS and invasive SCC is often challenging because focal biopsies of the vocal cords can miss an area of microinvasion and mucosal stripping of a vocal cord lesion results in a disoriented specimen that precludes a complete evaluation of the basement membrane region. However, both CIS and microinvasive SCC are treated the same, with either endoscopic transoral laser resection or RT.

Most vocal cord SCCs are either well or moderately well differentiated. In a few cases, SCCs with a spindle cell component may be observed. Verrucous carcinoma occurs on the vocal cords in about 1% to 2% of patients with carcinoma. Supraglottic SCCs are less differentiated; verrucous cancers are rare.

PATTERNS OF SPREAD

Supraglottic Larynx

Lesions may exhibit an exophytic growth pattern with little tendency to destroy cartilage or spread to adjacent structures. Others may infiltrate and destroy cartilage and eventually amputate the tip of the epiglottis. They tend to invade the vallecula, preepiglottic space, lateral pharyngeal walls, and the remainder of the supraglottis.

False vocal cord cancers are often submucosal. Those arising from the aryepiglottic fold tend to invade the medial wall of the pyriform sinus. An inferior invasion of the vocal cords is usually a late phenomenon, and subglottic extension occurs only in advanced lesions. Lesions that extend onto or below the vocal cords are at a high risk for cartilage invasion, even if the cords are mobile.[278]

Vocal Cord

The majority of lesions begin on the free margin and upper surface of the vocal cord. About two thirds are confined to one cord, usually the anterior two thirds of the cord. Extension to the anterior commissure is frequent. As the lesion enlarges, it extends to the ventricle, false cord, vocal process of the arytenoids, and subglottis. Cancers then invade the vocal ligament and thyroarytenoid muscles, eventually reaching the thyroid cartilage where they tend to grow up or down the paraglottic space rather than invade cartilage. The conus elasticus initially acts as a barrier to subglottic extension. Advanced lesions eventually invade through the thyroid cartilage or thyrocricoid membrane to enter the neck and/or thyroid gland.

Subglottic Larynx

Subglottic cancers involve the cricoid cartilage early, and cord fixation is common.

Lymphatic

Supraglottic

Lymphatic drainage is initially to the level II nodes, and then to levels III and IV.[20] The incidence of clinically positive nodes is 55% at diagnosis; 16% are bilateral.[20] Elective neck dissection will show pathologically positive nodes in 16% to 26% of cases; observation of the neck will be followed by the appearance of positive nodes in approximately 33% of cases.

Glottic

The incidence of clinically positive nodes at diagnosis varies with T stage: T1, ≤1%; T2, ≤5%; and T3 and T4, 20% to 30%.[279] Supraglottic spread is associated with metastasis to the level II nodes. Anterior commissure and subglottic invasion is associated with level III, level IV, and Delphian node involvement.[280]

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Subglottic

Lederman[281] reported a 10% incidence of clinically positive lymph nodes on admission. Spread is primarily to the Delphian nodes and the level IV nodes.

CLINICAL PICTURE

Presenting Symptoms

Vocal Cords

Carcinoma initially causes hoarseness. Pain, dysphagia, and airway obstruction may be observed with advanced cancers.

Supraglottic Larynx

Pain on swallowing, referred to the ear by the vagus nerve and the auricular nerve of Arnold, is a frequent initial symptom. A neck mass may be the first sign of a supraglottic cancer. Late symptoms include hoarseness, weight loss, foul breath, dysphagia, and aspiration.

Physical Examination

A determination of laryngeal mobility with a laryngeal mirror or fiber optic scope frequently requires multiple examinations because the subtle distinctions between mobile, partially fixed, and fixed cords are often difficult. Preepiglottic space invasion is best appreciated on CT.

Postcricoid extension may be suspected when the laryngeal "click" disappears on physical examination. Localized pain or tenderness to palpation over the thyroid cartilage is suggestive of invasion. Advanced tumors may penetrate through the thyroid ala and be felt as a bulge on the cartilage. A CT scan may detect cartilage invasion, but irregular calcification of the cartilage, coupled with volume averaging of the CT slice, creates technical problems in appreciating early cartilage invasion.

DIFFERENTIAL DIAGNOSIS AND STAGING

The differential diagnosis includes papillomas, polyps, vocal nodules, fibromas, and granulomas. Papillomas generally occur in children and young adults, and may persist into adulthood. Vocal polyps and nodules occur at the junction of the middle and anterior one third of the true vocal cords. There is usually a history of voice abuse followed by hoarseness. Vocal cord granulomas usually occur as a result of intubation and are located on or near the posterior commissure. Endoscopic removal may be necessary if medical therapy for gastroesophageal reflux provides no improvement, although this is rare.

The staging system for the primary tumor is depicted in Table 38.13.

TABLE 38.13

2010 American Joint Committee on Cancer Staging for Laryngeal Cancer

Primary Tumor (T)	
TX	Primary tumor cannot be assessed
T0	No evidence of primary tumor
Tis	Carcinoma in situ
Supraglottis	
T1	Tumor limited to one subsite of supraglottis with normal vocal cord mobility
T2	Tumor invades mucosa of more than one adjacent subsite of supraglottis or region outside the supraglottis (e.g., mucosa of base of tongue, vallecula, medial wall of pyriform sinus) without fixation of the larynx
T3	Tumor limited to larynx with vocal cord fixation and/or invades any of the following: postcricoid area, preepiglottic tissues, paraglottic space, and/or minor thyroid cartilage erosion (e.g., inner cortex)
T4a	Tumor invades through the thyroid cartilage and/or invades tissues beyond the larynx (e.g., trachea, soft tissues of neck including deep extrinsic muscles of the tongue, strap muscles, thyroid, or esophagus)
T4b	Tumor invades prevertebral space, encases carotid artery, or invades mediastinal structures
Glottis	
T1	Tumor limited to one (T1a) or both (T1b) vocal cord(s) (may involve anterior or posterior commissure) with normal mobility
T2	Tumor extends to supraglottis and/or subglottis, and/or with impaired vocal cord mobility
T3	Tumor limited to the larynx with vocal cord fixation, and/or invades paraglottic space, and/or minor thyroid cartilage erosion (e.g., inner cortex)
T4a	Tumor invades through the thyroid cartilage and/or invades tissues beyond the larynx (e.g., trachea, soft tissues of neck including deep extrinsic muscles of the tongue, strap muscles, thyroid, esophagus)
T4b	Tumor invades prevertebral space, encases carotid artery, or invades mediastinal structures
Subglottis	
T1	Tumor limited to the subglottis
T2	Tumor extends to vocal cord(s) with normal or impaired mobility
T3	Tumor limited to larynx with vocal cord fixation
T4a	Tumor invades cricoid or thyroid cartilage and/or tissues beyond the larynx (e.g., trachea, soft tissues of neck including deep extrinsic muscles of the tongue, strap muscles, thyroid, or esophagus)
T4b	Tumor invades prevertebral space, encases carotid artery, or invades mediastinal structures

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TREATMENT: VOCAL CORD CARCINOMA

Selection of Treatment Modality

Carcinoma In Situ

Vocal cord stripping may sometimes control CIS. Recurrence is frequent, and the vocal cord may become thickened and the voice hoarse with repeated stripping. We recommend RT for patients with multiple recurrences.[282]

Early Vocal Cord Lesions (T1, T2)

In most centers, RT is the initial treatment, with operation reserved for salvage of RT failures.[283] Although an open partial laryngectomy will produce comparable cure rates for selected T1 or T2 vocal cord lesions, RT is generally preferred because it is less expensive and voice quality is better. An endoscopic transoral laser resection is increasingly being used.[283] Using this technique, small midcord lesions may be treated. Voice quality depends on the extent of tissue removal and whether surgical resection involves the anterior commissure. An open partial laryngectomy or a total laryngectomy may be used as a salvage operation after RT failure.

Verrucous carcinomas are treated with a transoral laser resection or an open partial laryngectomy. Definitive RT is employed if the alternative is a total laryngectomy.

Advanced Vocal Cord Lesions (T3, T4)

Low volume cancers (≤3.5 mL) with stage III to IV disease are treated with definitive RT and concomitant chemotherapy.[284,285] Higher volume carcinomas are usually treated with a total laryngectomy, neck dissection, and postoperative RT or chemoRT.

Surgical Treatment

Stripping the cord implies transoral removal of the mucosa of the edge of the cord.

A cordectomy is an excision of the vocal cord and is usually performed via a transoral laser. The major advantages of laser excision are that it requires a day, as opposed to the 5.5 weeks that are necessary for RT, and RT may be reserved if the patient develops a second head and neck cancer.

A hemilaryngectomy is a partial laryngectomy allowing the removal of limited cord lesions with voice preservation. Restrictions include the involvement of one cord and up to 5 mm of the opposite cord, a partial fixation of one cord, and up to 9 mm of subglottic extension anteriorly and 5 mm posteriorly (to preserve the cricoid cartilage). Extension to the supraglottic or interarytenoid area is a contraindication. One arytenoid may be sacrificed; the reconstructed vocal cord must be fixed in the midline to prevent aspiration. The patient must have adequate pulmonary function. More extensive open partial laryngectomies have been described, such as the supracricoid partial laryngectomy.[286]

The last surgical alternative is a total laryngectomy with or without a neck dissection. The entire larynx is removed, the pharynx is reconstituted, and a permanent tracheostoma is created.

There are several options to accomplish voice rehabilitation after a total laryngectomy. Prosthetic devices (e.g., the Blom-Singer Voice Prosthesis) have been developed for insertion into a tracheoesophageal fistula, which permits the patient to speak without aspiration.[287] Voice rehabilitation was evaluated in 173 patients who underwent a total laryngectomy and postoperative RT at the University of Florida; 118 patients were evaluable 2 to 3 years after treatment and 69 patients were evaluated for 5 years or longer.[287] Methods of voice rehabilitation at 2 to 3 years and 5 years or more after surgery included: tracheoesophageal speech, 27% and 19%; artificial ("electric") larynx, 50% and 57%; esophageal, 1% and 3%; nonvocal, 17% and 14%; and no data, 5% and 7%, respectively.[287]

Irradiation Technique

RT for early vocal cord cancer is delivered by portals including only the primary lesion. Portals for T1 lesions extend from the thyroid notch superiorly to the inferior border of the cricoid; the posterior border depends on posterior extension of the tumor. Portals for T2 lesions are slightly larger, depending on the extent of the lesion. Patients receive 2.25 Gy per fraction once daily to 63 Gy (T1 and T2a) or 65.25 Gy (T2b).[279,288]

RT for T3 and T4 lesions include the primary lesion and the level II through IV and Delphian lymph nodes. The initial treatment is delivered at 1.2 Gy per fraction twice daily to 45.6 Gy. The portals are then reduced to include only the primary lesion; the final tumor dose is 74.4 Gy. Another option is 70 Gy in 35 fractions in over 30 treatment days. The low neck is treated through a separate anterior portal. IMRT may be useful to avoid a difficult low neck match in patients with a low-lying larynx.

Management of Recurrence

Worsening laryngeal edema suggests recurrence. Cord fixation usually implies local recurrence; fixation may rarely develop in the absence of recurrent disease.

RT failures (T1 to T2) are almost always salvaged by a cordectomy, a partial laryngectomy, or a total laryngectomy. The salvage rate for T3 lesions recurring after RT is approximately 60%.[285]

Salvage by RT-based treatment for recurrences or new tumors appearing after partial laryngectomy is about 50%. Isolated tracheostomal recurrences may be managed by RT, chemoRT, or surgery and postoperative RT-based treatment; the chance of cure is relatively low.[289] A multi-institutional surgical experience in the management of stomal recurrence was reported by Gluckman and coworkers.[289] Forty-one patients came to operation. The 2-year cause-specific survival was 24%. Patients with localized recurrences had a 5-year survival rate of 45%.

TREATMENT: SUPRAGLOTTIC LARYNX CARCINOMA

Selection of Treatment Modality

T1, T2, and low-volume (≤6 mL) T3 lesions are favorable and can be treated with definitive RT or a supraglottic laryngectomy. It is seldom necessary to combine RT and surgery for the management of the primary lesion; however, combined treatment may be indicated to control neck disease.

Patients who are candidates for a supraglottic laryngectomy must have lesions that are anatomically suitable, a resectable neck disease, and adequate pulmonary reserve to withstand aspiration. Because the likelihood of local control after RT is related to primary tumor volume, lesions >6 mL are treated with a partial laryngectomy.[290,291] The anatomic constraints include: no extension inferior to the apex of the ventricle, minimal or no involvement of the medial wall of the pyriform sinus, mobile cords, no cartilage invasion, and limited lateralized extension to the tongue base. Patients who are not candidates for the supraglottic laryngectomy are treated with RT; concomitant chemotherapy is added for those with stage III through IV disease.

When a patient presents with an early-stage primary lesion and N2B to N3 neck disease, a combined treatment is necessary to produce a high rate of neck control. Thus, the primary lesion is preferably treated with chemoRT, with neck dissection(s) added to the involved side(s) of the neck if necessary. If the patient has N1 or N2A neck disease and surgery is elected for the primary site, postoperative RT or chemoRT is only added because of unexpected findings (e.g., positive margins, multiple positive nodes, ECE). The probability of a good functional result is improved if the dose to the remaining larynx is limited to 55 Gy at 1.8 Gy per

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once-daily fraction. The involved neck may be boosted to a higher dose without irradiating the larynx.

Selected unfavorable T3 and T4 lesions that are mainly exophytic can be treated by chemoRT. Lesions unsuitable for RT are endophytic, high-volume cancers often associated with vocal cord fixation, which are managed by a total laryngectomy.

Surgical Treatment

Supraglottic Laryngectomy

The incision is usually an apron flap. The neck dissection is completed and left attached to the thyrohyoid membrane. The perichondrium of the larynx is elevated in continuity with the strap muscles and used to close the surgical defect. Saw cuts are made through the thyroid cartilage, and the pharynx is entered above the hyoid bone through the vallecula so the preepiglottic space is included in the specimen. The arytenoids and true vocal cords are preserved. If one arytenoid is sacrificed, the vocal cord is fixed in the midline to prevent aspiration. Suturing the perichondrium and muscle to the base of tongue closes the defect. The extended supraglottic laryngectomy may include resection of the base of tongue to the level of the circumvallate papillae as long as one lingual artery is spared.

Total Laryngectomy

The entire larynx and the preepiglottic space are resected en bloc and a permanent tracheostoma is fashioned. A portion of the thyroid gland is also removed if there is extralaryngeal or subglottic extension. The pharyngeal defect is closed, reestablishing a conduit from the pharynx into the esophagus.

Irradiation Technique

The primary lesion and both sides of the neck are included with opposed lateral portals. The inferior border of the portals depends on the inferior extent of the primary tumor; it is usually at the inferior border of the cricoid. The dose is 74.4 Gy in 62 twice-daily fractions; the lower neck nodes are irradiated through a separate anterior portal. Patients with ipsilateral positive nodes may be treated with IMRT to reduce the dose to the contralateral parotid and/or to avoid a difficult low neck match. An alternative is 70 Gy in 35 fractions over 30 treatment days.

Patients develop a sore throat, loss of taste, and moderate dryness during RT. Arytenoid edema may occur and produce the sensation of a lump in the throat. A tracheostomy is seldom necessary before the start of RT. Laryngeal edema may persist for up to a year. Neck dissection increases the degree of lymphedema; a bilateral neck dissection should be avoided, if possible.[292]

Combined Treatment Policies

If a total laryngectomy is required and the lesion is resectable, postoperative RT is preferred. The high-risk areas are usually the base of tongue and neck. The stoma is at risk when subglottic extension is present or if there is tumor in the low neck lymph nodes.

Management of Recurrence

Failures after supraglottic laryngectomy or RT frequently can be salvaged by further treatment. The salvage of recurrences that develop after total laryngectomy and adjuvant RT is uncommon.

TREATMENT: SUBGLOTTIC LARYNX CARCINOMA

Early lesions are treated with RT; advanced lesions are usually managed by a total laryngectomy and postoperative RT or chemoRT.

Results of Treatment

Vocal Cord Cancer

Surgical Results. Garcia-Serra et al.[282] reviewed 10 series containing 269 patients with CIS of the vocal cord treated with stripping; the weighted average 5-year local control and ultimate local control rates were 71.9% and 92.4%, respectively. Similarly, 10 series containing 177 patients treated with carbon dioxide laser revealed the following weighted average 5-year local control and ultimate local control rates: 82.5% and 98.1%, respectively.[282]

Thomas and coworkers[293] reported on 159 patients who underwent an open partial laryngectomy at the Mayo Clinic between 1976 and 1986. Of 159 patients, 17 had CIS; the remaining were T1 SCCs. Local recurrence developed in 11 patients (7%), and 9 eventually required a laryngectomy. Ten patients developed recurrent cancer in the neck, and distant metastases were observed in 10 patients.

A hemilaryngectomy, including the ipsilateral arytenoid, was reported by Som[294] for 130 cases of vocal cord carcinoma extending to the vocal process and face of the aryteroid. The cure rate was 74% for 104 patients with T2 lesions, and 58% for 26 patients with T3 cancers.

Foote and coworkers[295] reported on 81 patients who underwent a laryngectomy for T3 cancers at the Mayo Clinic between 1970 and 1981. Seventy-five patients underwent a total laryngectomy and six underwent a near-total laryngectomy; 53 received a neck dissection. No patient underwent adjuvant RT or chemotherapy. The 5-year rates of local–regional control, cause-specific survival, and absolute survival were 74%, 74%, and 54%, respectively.

Radiation Therapy Results. Garcia-Serra et al.[282] reviewed 22 series containing 705 patients with CIS of the vocal cord treated with RT and observed that the weighted average 5-year local control and ultimate local control rates were 87.4% and 98.4%, respectively.

The results of RT for 585 patients with T1 and T2 N0 SCC of the glottis treated by RT are presented in Table 38.14. The 5-year rates of neck control for the overall groups and for the subsets of patients who remained continuously disease free at the primary site were for T1a, 98% and 100%; for T1b, 99% and 100%; for T2a, 96% and 98%; and for T2b, 88% and 94%, respectively.[279]

The 5-year outcomes after RT alone (53 patients) versus surgery alone or combined with RT (65 patients) in a series of 118 patients with T3 fixed-cord glottic carcinomas treated at the University of Florida were for local–regional control, 62% versus 75% ($p = 0.10$); for ultimate local–regional control, 84% versus 82% ($p = 0.95$); for cause-specific survival, 75% versus 71% ($p = 0.26$); for overall survival, 55% versus 45% ($p = 0.119$); and for severe complications, 16% versus 15% ($p = 0.558$), respectively.[284] Hinerman et al.[296] recently updated the University of Florida experience and reported a 5-year local control rate of 63% for 87 patients with T3 fixed-cord glottic carcinomas. The likelihood of local control after RT is related to primary tumor volume and cartilage sclerosis.[297]

The probability of cure after treatment for T4 glottic carcinomas after surgery with or without adjuvant RT or definitive RT varies from 30% to 50% depending on patient selection.[296–303]

TREATMENT: SUPRAGLOTTIC LARYNX CANCER

The 5-year local control rates after definitive RT in a series of 274 patients treated between 1964 and 1998 at the University of Florida were for T1, 100% (n = 22); for T2, 86% (n = 125); for T3, 62% (n = 99); and for T4, 62% (n = 28).[304] The likelihood of local control and local control with a functional larynx is related to tumor volume; those with tumors ≤6 mL have a more favorable outcome

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TABLE 38.14

T1 to T2N0 Glottic Larynx: 5-Year Outcomes After Radiotherapy in 585 Patients

Stage	No. of Patients	Local Control	Ultimate Local Control	Local Control With Larynx Preservation	Cause-Specific Survival	Survival
T1A	253	94%	98%	95%	97%	82%
T1B	72	93%	97%	94%	99%	83%
T2A	165	80%	96%	81%	94%	76%
T2B	95	70%	93%	74%	90%	78%

Data from Chera BS, Amdur R, Morris CG, et al. T1N0 to T2N0 squamous cell carcinoma of the glottic larynx treated with definitive radiotherapy. *Int J Radiat Oncol Biol Phys* 2010;78:461–466.

than those with larger primary tumors.[291] The 5-year rates of local–regional control and cause-specific survival were for stage I, 100% and 100%; for stage II, 86% and 93%; for stage III, 64% and 81%; for stage IVA, 61% and 50%; and for stage IVB, 28% and 13%, respectively.[304] Of 274 patients, 12 (4%) experienced a severe acute or late complication, and 2 patients (1%) died as a consequence.

Lee and coworkers[305] reported on 60 patients who underwent a supraglottic laryngectomy and modified neck dissection at the M.D. Anderson Hospital between 1974 and 1987, of which 50 patients (83%) received postoperative RT. Local control was 100% and local–regional control was obtained in 56 of 60 patients (93%). The 5-year disease-free survival rate was 91%. Three of 60 patients (5%) required a complete laryngectomy for intractable aspiration.

Ambrosch and colleagues[306] reported on 48 patients treated with transoral laser resection for T1N0 (12 patients) and T2N0 (36 patients) supraglottic carcinoma. Twenty-six patients underwent a unilateral (11 patients) or bilateral (15 patients) neck dissection. Postoperative RT was administered to two patients (4%). The 5-year local control rates were 100% for pT1 cancers and 89% for pT2 malignancies. The 5-year recurrence-free survival and overall survival rates were 83% and 76%, respectively. No patient developed severe aspiration.

Complications of Treatment

Surgical Treatment

Repeated stripping of the cord may result in vocal cord fibrosis and hoarseness. Neel and coworkers[307] reported a 26% incidence of nonfatal complications for cordectomy. Immediate postoperative complications included atelectasis and pneumonia, severe subcutaneous emphysema in the neck, bleeding from the tracheotomy site or larynx, wound complications, and airway obstruction requiring a tracheotomy. Late complications included the removal of granulation tissue by a direct laryngoscopy to exclude recurrence, extrusion of cartilage, laryngeal stenosis, and obstructing laryngeal web.

The postoperative complications of hemilaryngectomy include aspiration, chondritis, wound slough, inadequate glottic closure, and anterior commissure webs.

The complication rate following supraglottic laryngectomy is about 10%, including fistula formation, aspiration, chondritis, dysphagia, dyspnea, and carotid rupture.[304]

The postoperative complications of a total laryngectomy may include perioperative death, hemorrhage, fistula, chondritis, wound breakdown, carotid rupture, dysphagia, and pharyngoesophageal stenosis.

Radiation Therapy

Soft-tissue necrosis leading to chondritis occurs in about 1% of patients. Soft-tissue and cartilage necroses mimic recurrence with hoarseness, pain, and edema; a laryngectomy may be recommended for fear of recurrent cancer, even though biopsies show only necrosis. Chera et al.[279] recorded severe complications after definitive RT in 10 (1.7%) of 585 patients treated for T1 to T2N0 glottic SCCs.

Combined Treatment

The major late effects of combined treatment are an increased fibrosis of soft tissues, stomal stenosis, and pharyngeal stricture.

HYPOPHARYNX: PHARYNGEAL WALLS, PYRIFORM SINUS, AND POSTCRICOID PHARYNX

Both the oropharyngeal and hypopharyngeal walls will be considered together because there is no distinct difference in the presentation or treatment. The majority of hypopharyngeal lesions originate in the pyriform sinus. Postcricoid carcinomas are uncommon.

ANATOMY

The epithelium of the pharyngeal mucous membrane is squamous. The dividing point between the nasopharynx and posterior pharyngeal wall is the Passavant ridge, a muscular ring that contracts to close the nasopharynx during swallowing. Between the constrictor muscles and the prevertebral fascia covering the longitudinal prevertebral muscles is a thin layer of loose areolar tissue, the retropharyngeal space. The entire thickness of the posterior pharyngeal wall from the mucous membrane to the anterior vertebral body is no more than 1 cm in the midline. Lateral to the pharyngeal wall are the vessels, nerves, and muscles of the parapharyngeal space. The constrictor muscles are relatively thin and do not present much of an obstacle to tumor penetration. There is a variable weak spot in the lateral pharyngeal wall just below the hyoid where the middle and the inferior constrictor muscles fail to overlap. The lateral wall in this area is composed of the thin thyrohyoid membrane, which is penetrated by the vessels, nerves, and lymphatics of the laryngopharynx.

The pharyngeal walls are continuous with the cervical esophagus below; the transition to cervical esophagus is below the arytenoids (C4). The transition zone, which is 3 cm to 4 cm in length, is the postcricoid hypopharynx.

The lateral pharyngeal wall is a narrow strip of mucosa that lies behind the posterior tonsillar pillar in the oropharynx, is partially interrupted by the pharyngoepiglottic fold, and then continues into the hypopharynx, where it becomes the lateral wall of the pyriform sinus. The posterior pharyngeal wall is 4 cm to 5 cm wide and 6 cm to 7 cm in height.

The superior margin of the pyriform sinus is the pharyngoepiglottic fold and the free margin of the aryepiglottic fold. The superolateral margin of the pyriform sinus is an oblique line along the lateral pharyngeal wall opposite the aryepiglottic fold. Thus,

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the pyriform sinus has three walls: the anterior, lateral, and medial (there is no posterior wall). The pyriform sinus tapers inferiorly to the apex and terminates variably at a level between the superior and inferior borders of the cricoid cartilage. The superior limit of the pyriform sinus is opposite the hyoid. The thyrohyoid membrane is lateral to the upper portion of the pyriform sinus, and the thyroid cartilage, cricothyroid membrane, and cricoid cartilage are lateral to the lower portion. The internal branch of the superior laryngeal nerve, a branch of the vagus, lies under the mucous membrane on the anterolateral wall of the pyriform sinus. The auricular branch is sensory to the skin of the back of the pinna and the posterior wall of the external auditory canal.

The postcricoid pharynx is funnel shaped to direct food into the esophagus. The superior margin begins just below the arytenoids. The anterior wall lies behind the cricoid cartilage and is the posterior wall of the lower larynx. The posterior wall is a continuation of the hypopharyngeal walls. The recurrent laryngeal nerve ascends in the tracheoesophageal groove, entering the larynx posterior to the cricothyroid articulation at the junction of the hypopharynx and esophagus. Internal branches of the superior laryngeal nerve extend inferiorly anterior to the mucosa of the piriform sinuses.

PATHOLOGY

More than 95% of malignant tumors are SCCs. CIS is commonly seen at the edge of pharyngeal wall SCCs; multifocal skip areas of CIS may make it difficult to obtain clear margins if excision is done. Minor salivary gland tumors are rare.

PATTERNS OF SPREAD

Posterior Pharyngeal Wall

SCCs of the posterior wall have a tendency to remain on the posterior wall, grow up or down the wall, and infiltrate posteriorly; they seldom spread circumferentially to the lateral walls. Early lesions are red and ulcerate as they progress. The tumor may spread up the pillars, eventually reaching the palate and nasopharynx. Advanced lesions tend to terminate inferiorly at the level of the arytenoids. Direct invasion of the cervical vertebrae or skull base is uncommon.

Lateral Pharyngeal Wall

Early tumors may be well-defined exophytic lesions. As they advance, they tend to penetrate laterally through the constrictor muscle, thus entering the lateral pharyngeal space or the soft tissues of the neck.

Pyriform Sinus

Early lesions usually appear as nodular mucosal irregularities. Medial wall lesions may grow superficially along the aryepiglottic fold and arytenoids, or invade directly into the false cord and aryepiglottic fold. Medial wall lesions also extend posteriorly to the postcricoid region, cricoid cartilage, and to the opposite pyriform sinus. Extensive submucosal spread is characteristic. There is frequently an area of central ulceration. The vocal cord becomes fixed because of infiltration of the intrinsic muscles of the larynx, the cricoarytenoid joint or muscle, or less commonly, the recurrent laryngeal nerve. Spread into the cervical esophagus is a late event.

Lesions arising on the lateral wall tend toward early invasion of the posterior thyroid cartilage and the posterior superior cricoid cartilage and, eventually, invade the thyroid gland. Involvement of the pyriform sinus apex is associated with an increased risk of thyroid cartilage invasion.[308] Lesions of the lateral walls tend to spread submucosally to the posterior pharyngeal wall.

Postcricoid Pharynx

Early postcricoid lesions are rare. Lesions arising from the posterior wall tend to remain on the posterior wall. Lesions arising from the anterior wall tend to invade the posterior cricoarytenoid muscle and the cricoid and arytenoid cartilages. Advanced tumors eventually encircle the lumen.

Lymphatics

Pharyngeal Walls

The lymphatics of the pharyngeal walls terminate primarily in the jugular chain and secondarily in the level V nodes. The level II nodes are most often involved. Lindberg[20] reported 59% clinically positive nodes at diagnosis; 17% were bilateral. Retropharyngeal lymph node involvement is frequent.

Pyriform Sinus

The drainage is mainly to the jugular chain with a relatively small proportion to the level V nodes. The level II nodes are most commonly involved, but level III involvement occurs without level II metastases. At diagnosis, 75% of patients have clinically positive nodes, and at least 10% have bilateral nodes. There is no difference in the risk of lymph node metastases by T stage. The incidence of subclinical neck disease probably exceeds 50%.[309]

CLINICAL PICTURE

Tumors that are lateralized to the lateral pharyngeal wall or pyriform sinus produce a unilateral sore throat. Dysphagia, ear pain, and voice changes occur later. A neck mass may be the presenting complaint.

Lesions of the apex of the pyriform sinus or postcricoid area produce a pooling of secretions, indicating obstruction of the gullet. Arytenoid edema and an inability to see into the apex of the pyriform sinus may be observed.

STAGING

The staging system for the primary tumor is depicted in Table 38.15.

TABLE 38.15

Hypopharynx: 2010 American Joint Committee on Cancer Staging System for the Primary Tumor

T1	Tumor limited to one subsite of hypopharynx and 2 cm or less in greatest dimension
T2	Tumor invades more than one subsite of hypopharynx or an adjacent site, or measures more than 2 cm but not more than 4 cm in greatest diameter without fixation of the hemilarynx
T3	Tumor more than 4 cm in greatest dimension or with fixation of the hemilarynx or extension to esophagus
T4a	Tumor invades thyroid/cricoid cartilage, hyoid bone, thyroid gland, or central compartment soft tissue[a]
T4b	Tumor invades the prevertebral fascia, encases the carotid artery, or involves mediastinal structures

[a] Central compartment soft tissue includes the prelaryngeal strap muscles and subcutaneous fat.

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TREATMENT

Selection of Treatment Modality

Posterior Pharyngeal Wall

RT produces cure rates similar to those produced by surgery alone or combined with RT, and with less morbidity. Thus, almost all cancers are treated with RT.

Lateral Pharyngeal Wall

The preferred treatment is definitive RT.

Pyriform Sinus

T1 and low-volume (≤6 mL), exophytic T2 cancers with normal cord mobility can be treated either by RT or a partial laryngopharyngectomy.[310] RT is preferred because it is associated with less morbidity.

Selected high-volume endophytic T2 and T3 lesions with normal or reduced mobility may be suitable for chemoRT. The swallowing outcomes after concurrent chemoRT may be less optimal than those seen in the oropharynx and larynx.[311]

The remainders are best treated with a total laryngopharyngectomy, neck dissection, and postoperative RT or chemoRT. Patients presenting with an extensive primary lesion and extensive neck metastases are frequently offered palliative therapy.

Surgical Treatment

Posterior Pharyngeal Wall

If the lesion is high on the posterior wall, a transoral approach can be used. Lower lesions were traditionally accessed via a transhyoid approach, a lateral pharyngotomy, or a midline mandibulolabial glossotomy. More recently, transoral laser microsurgical resection has been employed to reduce the morbidity associated with open approaches, which also frequently require tracheotomy. Dissection extends deep to the tumor down to the prevertebral fascia; smaller defects heal by secondary intention without a skin graft, whereas larger defects may require a radial forearm free flap.

Pyriform Sinus

Partial Laryngopharyngectomy. A partial laryngopharyngectomy removes the false cords, epiglottis, aryepiglottic fold, and pyriform sinus; one arytenoid may be removed when necessary. The vocal cords are preserved. The following findings contraindicate a partial laryngopharyngectomy: extension to the apex of the pyriform sinus, a fixed cord, extension to contralateral arytenoid, poor pulmonary function, and large, fixed lymph nodes.

Total Laryngopharyngectomy. A total laryngopharyngectomy removes the larynx and varying amounts of the pharyngeal wall. Advanced lesions require excision of nearly the entire circumference. The pharynx is reestablished by primary closure after a partial pharyngectomy; reconstruction is accomplished with a pectoralis major myocutaneous flap or a radial forearm free flap.

Postcricoid Pharynx

A total laryngopharyngectomy with reconstruction, generally using a pectoralis major myocutaneous flap or free flap, is performed. If the lesion extends into the cervical esophagus, a gastric pull-up or jejunal free flap may be necessary.

Irradiation Technique

Posterior Pharyngeal Wall

The RT technique is opposed lateral fields to include the primary lesion and the regional nodes. Because these lesions tend to "skip" areas, the entire posterior pharyngeal wall is included initially. If the lesion extends near the arytenoids, the postcricoid pharynx, pyriform sinuses, and upper cervical esophagus are included. The retropharyngeal nodes are included even if the neck is N0. When the field is reduced at 45 Gy to avoid the spinal cord, the posterior border of the portal is placed just anterior to the spinal cord.[312] The dose is 74.4 to 76.8 Gy, at 1.2 Gy per fraction twice daily, in a continuous course. Another option is 70 Gy in 35 fractions over 30 treatment days. IMRT is useful to reduce the dose to one or both parotids. Concomitant chemotherapy should be included for stage III through IV cancers.

Pyriform Sinus

Parallel-opposed lateral portals are used to encompass the primary lesion and regional nodes on both sides. The superior border is placed 2 cm above the tip of the mastoid to cover the most superior jugular chain and the retropharyngeal lymph nodes. The posterior border encompasses the level V nodes. Clinically positive nodes behind the plane of the spinal cord require an electron boost. The anterior border is usually placed about 0.5 to 1 cm behind the anterior skin edge if it is possible to do so and adequately encompass the tumor. The inferior border is 2 cm below the inferior border of the cricoid. The remaining lower neck lymph nodes are treated through an en face portal. The doses are the same as for the posterior pharyngeal wall. IMRT is an option if the tumor can be adequately encompassed while sparing the contralateral salivary gland(s) and/or to avoid a difficult low neck match.

Combined Treatment Policies

Posterior Pharyngeal Wall

An operation should usually precede RT when a combination is selected, unless a gastric pull-up is planned.

Pyriform Sinus

Following a total laryngopharyngectomy with or without neck dissection, RT is usually recommended for indications previously outlined. RT or chemoRT is used prior to operation for patients with a large fixed node. The dose to the primary tumor ranges from 45 to 50 Gy; the fixed node(s) is boosted to 60 to 75 Gy.

Management of Recurrence

Posterior Pharyngeal Wall

Recurrence after RT may be limited to the posterior pharyngeal wall and may be suitable for surgical excision, with occasional salvage. There is frequently a persistent ulcer after RT for advanced lesions; it should be considered evidence of persistent disease if it does not heal. Surgical excision is limited posteriorly by the prevertebral fascia. RT salvage of a surgical failure is unusual.

Pyriform Sinus

The hallmark of local recurrence after RT is persistent edema, pain, and fixation of laryngeal structures. A direct laryngoscopy is required, but the biopsy may be negative. A CT and/or PET scan is often helpful for distinguishing local recurrence from necrosis. It may be necessary to recommend a total laryngopharyngectomy for salvage without a positive biopsy.

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Recurrence after a total laryngopharyngectomy is usually in the soft tissues of the neck, the untreated opposite neck, the base of tongue, or stoma. Surgical failures after a partial laryngopharyngectomy for early lesions may be salvaged by a total laryngopharyngectomy. Failures after a total laryngopharyngectomy are rarely salvaged.

RESULTS OF TREATMENT

Pharyngeal Wall

The 5-year local control rates and ultimate local control rates after RT at the University of Florida for 170 patients were for T1 (n = 14), 93% and 93%; for T2 (n = 51), 84% and 91%; for T3 (n = 75), 60% and 62%; and for T4 (n = 30), 44% and 44%, respectively.[312] The 5-year local–regional control and cause-specific survival rates were for stage I, 88% and 88%; for stage II, 85% and 89%; for stage III, 49% and 44%; and for stage IV, 44% and 35%, respectively.[312]

Pyriform Sinus

The results of treatment for 80 patients with carcinoma of the pyriform sinus treated at Washington University by preoperative RT followed by a partial laryngopharyngectomy are shown in Table 38.16.[313] Seventy patients had the equivalent of AJCC T1 lesions (disease limited to the pyriform sinus), 10 patients had disease extending beyond the pyriform sinus, and none had invasion of the apex of the pyriform sinus. The cause of death was cancer in 26%, complications of treatment in 14%, and intercurrent disease in 20%. The 5-year absolute survival was 25 of 66 patients (38%) (JE Marks, Personal communication, 1979).

The results of treatment for 57 patients from the same institution who were treated by preoperative RT followed by total laryngectomy and partial pharyngectomy are depicted in Table 38.16.[313] Thirty-five patients had lesions confined to the pyriform sinus (AJCC T1) and the remainder had extension beyond the pyriform sinus (AJCC T2 to T4). The cause of death was cancer in 56% of patients, complications of treatment in 11% of patients, and intercurrent disease in 18% of patients.

TABLE 38.16

Carcinoma of the Pyriform Sinus: Results of Treatment by Low Dose Radiation Therapy Plus Partial Laryngopharyngectomy or Total Laryngectomy and Partial Pharyngectomy (Washington University, St. Louis, 1964–1974)

Result	PLP (80 Patients)[a]	TLP (57 Patients)[b]
Local recurrence ± neck recurrence	14%[c]	14%
Neck recurrence ± distant metastases (primary controlled)	9%	23%
Distant metastases alone	11%	21%
5-year actuarial survival (no evidence of disease)	40%	22%

[a] T1, 70 patients; T2–T4, 10 patients (AJCC staging).
[b] T1, 35 patients; T2–T4, 22 patients (AJCC staging).
[c] Four patients salvaged.
PLP, partial laryngopharyngectomy; TLP, total laryngopharyngectomy.
Data from Marks JE, Kurnick B, Powers WE, Ogura JH. Carcinoma of the pyriform sinus: an analysis of treatment results and patterns of failure. *Cancer* 1978;41:1008–1015.

The 5-year local control rates for 123 patients treated with definitive RT for T1 (23 patients) and T2 (100 patients) pyriform sinus SCCs were for T1, 85%; and for T2, 85%, respectively.[311] The 5-year rates of local–regional control and cause-specific survival were for stage I to II, 86% and 85%; for stage III, 65% and 73%; for stage IVA, 83% and 62%; and for stage IVB, 24% and 22%, respectively.[311] The 5-year distant metastasis-free survival rates were for N0, 96%; for N1, 88%; for N2, 68%; and for N3, 55%.

COMPLICATIONS OF TREATMENT

Posterior Pharyngeal Wall

Surgical Treatment Complications

Marks and coworkers[314] reported a 14% operative mortality plus major complications including pharyngocutaneous fistula (31%) and carotid rupture (14%) for patients treated with preoperative RT, 25 to 30 Gy.

Radiation Therapy Complications

Mendenhall and coworkers[312] observed 9 fatal complications (5%) in 170 patients who were treated at the University of Florida. Twenty-five patients (15%) experienced nonfatal severe complications including permanent feeding tube (17 patients), soft tissue and/or bone necrosis (7 patients), and permanent tracheostomy (1 patient).

Pyriform Sinus

Surgical Treatment Complications

The complications of a partial laryngopharyngectomy included a 12% operative mortality, fistula, aspiration, and dysphagia.[313] The complications of total laryngopharyngectomy included a treatment-related mortality of 11%, fistula, and pharyngeal stenosis.[313] The complication rate is increased by the addition of RT.

Radiation Therapy Complications

The major RT complication is laryngeal necrosis. Rabbani et al.[311] reported the following rates of moderate-to-severe complications in 123 patients: acute (2%); late (9%); and postoperative (5%).

Complications of Salvage Treatment

Attempted surgical salvage of RT failures has a significant operative morbidity and mortality; few patients are cured.

NASOPHARYNX

NPCs are uncommon in the United States. The Chinese have a high frequency; American-born second-generation Chinese maintain the risk of NPC. NPCs have been shown to have an association with elevated titers of EBV, which is independent of geography.[315] There is a 3 to 1 ratio of predominance in men. The age distribution for NPC is younger than for other head and neck sites; about 20% of patients are younger than 30 years of age.

ANATOMY

The nasopharynx is roughly cuboidal in shape. It is contiguous with the nasal cavity, inferiorly with the oropharynx, and laterally with the middle ears by way of the eustachian tubes.

The mucosa of the roof and posterior wall is often irregular because of the pharyngeal bursa, adenoids, and pharyngeal hypophysis; it tends to become smooth with age.

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The lateral walls include the eustachian tube openings with the fossa of Rosenmüller, located behind the torus tubarius. The superolateral muscular wall of the nasopharynx is incomplete. The floor of the nasopharynx is incomplete and consists of the upper surface of the soft palate.

Lymphatics

There is an extensive submucosal lymphatic capillary plexus. The tumor spreads along three different pathways: the jugular chain, the spinal accessory chain, and the retropharyngeal pathway.[316] The lateral retropharyngeal nodes lie in the retropharyngeal space medial to the carotid artery. Directly behind the nodes are the lateral masses of C1 and C2. Inconstant lymphatic vessels may drain directly to the level III and V nodes.[13]

PATHOLOGY

Carcinomas compose about 85% and lymphomas about 10% of the malignant lesions. NPCs are classified as follows: keratinizing squamous cell carcinoma (WHO type I); nonkeratinizing carcinoma (WHO type II), and undifferentiated (WHO type III) basaloid SCC. Lymphoepithelioma is included in the WHO type II and III categories. A miscellaneous group of malignant tumors includes melanoma, plasmacytoma,[270] juvenile angiofibroma,[14] carcinosarcoma, sarcomas, nonchromaffin paragangliomas, and minor salivary gland tumors.

PATTERNS OF SPREAD

Primary

Inferior extension along the lateral pharyngeal walls and tonsillar pillars occurs in almost one third of patients. Extension into the posterior nasal cavity is frequent but is usually limited to less than 1 cm. Invasion of the posterior ethmoids, maxillary antrum, and/or orbit occurs fairly often. Skull base invasion is recognized radiographically in at least 25% of patients. The sphenoid sinus frequently is invaded. The tumor may erode through the foramen ovale, lacerum, and/or spinosum. The tumor eventually reaches the cavernous sinus and has access to CNs II to VI.

The lateral muscular wall of the nasopharynx is incomplete superiorly. The defect, termed the sinus of Morgagni, is transversed by the cartilaginous eustachian tube and the levator palatine muscle, providing access for NPCs to the lateral pharyngeal space and skull base.

Lymphatics

There is an 80% to 90% incidence of metastatic neck nodes on presentation; approximately 50% are bilateral. Low-grade SCCs produce fewer metastases (73%) than high-grade carcinomas (92%). Metastases to submental and occipital nodes may appear when there is blockage of the common lymphatic pathways either by massive neck disease or by an untimely neck dissection.

CLINICAL PICTURE

The most common presenting complaint is a painless upper neck mass. Nasal obstruction, epistaxis, sore throat, and otitis media may be observed. Facial pain may be referred from any of the three divisions of the trigeminal nerve, usually V3. Occipital or temporal headaches frequently are seen. Proptosis occurs with posterior orbital invasion. Trismus is due to the invasion of the pterygoid region.

Neurologic symptoms and signs occur in about 25% of patients. Involvement of CNs II to VI indicates extension into the cavernous sinus. CNs IX to XII and the sympathetic chain are involved in the lateral pharyngeal space.

An examination of the nasopharynx will show a lesion on the lateral wall or roof. Early lesions may be submucosal. Lymphomas tend to remain submucosal until quite large. The tumor infrequently grows very far down the posterior pharyngeal wall. The posterior tonsillar pillars may bulge into the oropharynx if an enlarged node develops in the lateral pharyngeal space. CN VI is the one most commonly involved.

STAGING

The AJCC staging system is depicted in Table 38.17.

TREATMENT

Selection of Treatment Modality

The treatment of almost all NPCs is RT-based because complete surgical resection is usually not feasible. Neck dissection is used less often in the management of neck disease because of the relatively high success rate with RT or chemoRT alone. A small adenocarcinoma or sarcoma may be excised. Juvenile angiofibromas are preferably excised because of the young age of the patient, although the tumors are quite successfully cured by RT when a complete resection is unlikely or dangerous.[14] Patients with advanced disease should receive concomitant chemotherapy.[190,192,201,317,318]

Irradiation Technique

If the tumor is thought to be limited to the nasopharynx or to have minimal soft-tissue extension, the following areas are included in the treatment volume: (1) the nasopharynx, (2) the posterior 2 cm of the nasal cavity, (3) the posterior ethmoid sinuses, (4) the entire sphenoid sinus and basioccipital bone, (5) the cavernous sinus, (6) the base of skull (7 to 8 cm width encompassing the foramen ovale, carotid canal, and foramen spinosum laterally), (7) the pterygoid fossae, (8) the posterior one third of the maxillary sinus, (9) the oropharyngeal wall to the level of the mid tonsillar fossa, (10) the retropharyngeal nodes, and (11) the neck nodes on both sides.

Extension to the skull base or involvement of CNs II to VI requires the superior border be raised to include the entire pituitary, the base of the brain in the suprasellar area, the adjacent middle cranial fossa, and the posterior portion of the anterior cranial fossa. Patients with anterior invasion into the orbit, ethmoids, or maxillary sinus require an individualized plan to produce a satisfactory dose distribution. The use of 3-dimensional CT-based treatment planning allows for the use of more conformal fields. IMRT is useful to improve coverage of the poststyloid parapharyngeal space and to reduce the dose to the parotid glands and the temporal lobes to reduce long-term morbidity. We currently treat patients to 74.4 at 1.2 Gy per fraction twice daily.

Neck Nodes. The entire neck is irradiated to the level of the clavicles. The retropharyngeal nodes are included in the treatment of the primary lesion. The upper neck nodes are included in the primary fields to the level of the thyroid notch. In the case of an N0 neck, the posterior margin is placed about 1 to 2 cm behind the posterior border of the sternocleidomastoid to encompass the high level V nodes and level 2 nodes. The portals are extended to include the submental area only if there is disease in the level IB nodes or if the patient had a neck dissection prior to RT. The lower neck is treated through an anterior portal with a shield over the larynx.

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TABLE 38.17

2010 American Joint Committee on Cancer Staging for Nasopharyngeal Cancer

Primary Tumor (T)	
T1	Tumor confined to the nasopharynx, or tumor extends to oropharynx and/or nasal cavity without parapharyngeal extension[a]
T2	Tumor with parapharyngeal extension[a]
T3	Tumor involves bony structures of skull base and/or paranasal sinuses
T4	Tumor with intracranial extension and/or involvement of cranial nerves, hypopharynx, orbit, or with extension to the infratemporal fossa/masticator space

[a] Parapharyngeal extension denotes posterolateral infiltration of tumor.

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Regional Lymph Nodes (N)	
NX	Regional lymph nodes cannot be assessed
N0	No regional lymph node metastasis
N1	Unilateral metastasis in lymph node(s), 6 cm or less in greatest dimension, above the supraclavicular fossa and/or unilateral or bilateral, retropharyngeal lymph nodes, 6 cm or less, in greatest dimension[a]
N2	Bilateral metastasis in cervical lymph node(s), 6 cm or less in greatest dimension, above the supraclavicular fossa[a]
N3	Metastasis in a lymph node(s),[a] >6 cm and/or to supraclavicular fossa
N3a	Greater than 6 cm in dimension
N3b	Extension to the supraclavicular fossa[b]

[a] Midline nodes are considered ipsilateral nodes.
[b] Supraclavicular zone or fossa is relevant to the staging of nasopharyngeal carcinoma and is the triangular region originally described by Ho. It is defined by three points: (1) the superior margin of the sternal end of the clavicle, (2) the superior margin of the lateral end of the clavicle, and (3) the point where the neck meets the shoulder. Note that this would include caudal portions of levels IV and VB. All cases with lymph nodes (whole or part) in the fossa are considered N3b.

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Stage Grouping			
0	Tis	N0	M0
I	T1	N0	M0
II	T1 T2 T2	N1 N0 N1	M0 M0 M0
III	T1 T2 T3 T3 T3	N2 N2 N0 N1 N2	M0 M0 M0 M0 M0
IVA	T4 T4 T4	N0 N1 N2	M0 M0 M0
IVB	Any T	N3	M0
IVC	Any T	Any N	M1

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Acute Sequelae. A sore throat begins at the end of the second week of therapy and persists for 2 to 3 months after the completion of RT. A xerostomia is always present. Loss of taste and appetite is often profound; both return 1 to 6 months after completion of RT. Obstruction of the eustachian tubes may occur with secondary otitis media and hearing loss. Polyethylene tubes inserted through the eardrums to drain the middle ears can correct this condition. The obstruction often improves after a few months. Severe nausea and vomiting are uncommon.

Management of Recurrence

The majority of recurrent SCCs are diagnosed within 2 years, but lymphoepithelioma may recur many years after treatment. Headache and CN palsies usually indicate recurrence. Retreatment for local recurrences with limited RT portals and/or intracavitary brachytherapy may be rewarding, particularly if the recurrence is due to a marginal miss or low dose.[319,320]

Results of Treatment

Lee and co-workers[321] reported the following 10-year outcomes in a series of 5,037 patients treated with RT at the Queen Elizabeth Hospital, Hong Kong, between 1976 and 1985: local control, 61%; regional control, 64%; distant metastasis-free survival, 59%; and survival, 42%. Leung et al.[322] reported the following 5-year local control rates in a series of 1,070 patients: T1, 88%; T2A, 87%; T2B, 82%; T3, 69%; and T4, 69%. Chua et al.[323] evaluated 290 patients and found that primary tumor volume of more than 60 mL was associated with a lower likelihood of local control after RT. Teo and colleagues[324] evaluated a series of 903 patients treated at the Prince of Wales Hospital, Hong Kong, and observed that local control was adversely affected by advanced patient age, skull base invasion, and CN involvement. Prognostic factors associated with an increased rate of distant metastases and poor survival were male sex, skull base and CN(s) involvement, advanced neck stage, nodal fixation, and bilateral neck nodes.[324] The 5-year outcomes for 82 patients treated at the University of Florida were for local control, 78%; for regional control, 90%; for local–regional control, 76%; for distant metastasis-free survival, 80%; for cause-specific survival, 66%; and for survival, 57%.[325] Table 38.9 summarizes the results of selected randomized trials comparing chemoRT versus RT alone.

Follow-Up

The follow-up includes careful observation and laboratory testing for possible thyroid and/or pituitary hypofunction. Dental care must be closely monitored because of xerostomia.

Complications of Treatment

Primary or secondary hypopituitarism (from a hypothalamic lesion) has been reported. Brain necrosis is rare. Hypothyroidism may result from either a direct effect on the thyroid gland or an indirect effect on the pituitary. A transient CNS syndrome may appear 2 to 3 months after RT and would require several months to resolve. General weakness and extreme fatigue may be symptoms of low serum cortisol levels. Radiation myelitis of the cervical cord or brain stem is the most severe CNS complication. IMRT may be used to reduce the dose to the CNS, particularly the temporal lobes.

Trismus may occur because of fibrosis of the pterygoid muscles. Palsy of CNs IX to XII may occur several years after RT and is related to nerve entrapment in the lateral pharyngeal space. Eye complications (e.g., retrobulbar optic neuritis) may develop owing to RT of the optic nerve.[326] RT of the posterior eyeball to high doses may produce a retinopathy.[327]

NASAL VESTIBULE, NASAL CAVITY, AND PARANASAL SINUSES

Tumors of the nasal vestibule are considered separately from nasal cavity tumors because they are essentially skin cancers and have a different natural history. Primary tumors arising from the nasal cavity and paranasal sinuses are considered together because the lesions are frequently advanced when first seen and it is not always possible to determine the site of origin.

Cancer of the nasal cavity or paranasal sinuses is a relatively rare problem, with a yearly risk factor estimated at approximately one case for every 100,000 people. They occur more often in men and usually appear after the age of 40 except for minor salivary gland tumors and esthesioneuroblastomas, which may appear before the age of 20.[328] Nasal cavity and ethmoid sinus adenocarcinomas have been linked to occupations associated with wood dust, such as the furniture industry, sawmill work, and carpentry. Other occupations with dust-filled work environments, such as shoe making, baking, and the flour milling industry, also have been implicated.[12]

Carcinomas of the sphenoid and frontal sinuses are rare.

Anatomy

The nasal vestibule is the entrance to the nasal cavity. It is lined by skin in which there are numerous hair follicles and sebaceous glands. The vestibule is a three-sided, pear-shaped cavity about 1.5 cm in diameter that ends posteriorly at the limen nasi. The alar cartilages form the anterolateral wall. The medial wall is the columella, formed by the medial wing of the alar cartilage and the anterior portion of the cartilaginous septum. The floor is the maxilla.

The nasal cavity begins at the limen nasi and ends at the posterior nares, where it communicates with the nasopharynx. The lateral walls are composed of thin bony folds that project into the nasal cavity: the inferior, medial, and superior turbinates. The nasolacrimal duct enters the nasal cavity beneath the inferior turbinate. The frontal sinus and ethmoid bullae connect to the nasal cavity with openings that lie under the middle turbinate. The sphenoid sinus communicates with the nasal cavity by an opening on the anterior wall of the sinus. Approximately 20 branches of the olfactory nerves enter the nasal cavity through the cribriform plate; nerve fibers are distributed over the upper one third of the septum and the superior nasal turbinate. The epithelium is nonciliated columnar. The lower half of the nasal cavity is the respiratory portion, and the epithelium is ciliated columnar. There are numerous collections of lymphoid tissue and mucous glands beneath the epithelium.

The maxillary sinuses are single pyramidal cavities. The medial wall is the lateral wall of the nasal cavity and has one or two openings communicating with the middle meatus under the medial turbinate. The inferior wall is the hard palate. The posterolateral wall is related to the zygomatic process and the pterygomaxillary space. The superior wall is the orbital floor.

The frontal sinuses are two irregular, asymmetrical air cavities separated by a thin bony septum. They connect to the middle meatus of the nasal cavity by the frontonasal duct. They are separated from the anterior ethmoid cells by thin bony walls. The posterior wall separating the frontal sinus from the anterior cranial fossa is relatively thick.

The ethmoid sinuses consist of a number of air cells lying between the medial walls of the orbits and the lateral wall of the nasal cavity. The lateral wall is the thin porous lamina papyracea. Medially, the ethmoid air cells bulge into the lateral wall of the nasal cavity. The ethmoid cells communicate with the nasal cavity in the middle meatus. These bony walls are thin and easily traversed by the tumor. The ethmoid air cells extend far anteriorly; the lacrimal bone covers the anterior cells laterally. The midline perpendicular plate of the ethmoid separates the right and left ethmoid cells anatomically. There is no anatomic barrier between the anterior, middle, and posterior ethmoids.

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The sphenoid sinus is a midline structure in the body of the sphenoid bone. The pituitary lies above, the cavernous sinuses laterally, the nasal cavity and ethmoid sinuses in front, and the nasopharynx beneath. The clivus and brain stem lie posteriorly. The pneumatization is variable and can extend into all portions of the sphenoid bone. The right and left sinuses are partially separated by an incomplete septum. The sphenoid sinus connects anteriorly with the nasal cavity in the sphenoethmoidal recess.

Lymphatics

Nasal Vestibule. The lymphatic trunks run to the level IB nodes. There is a small risk for involvement of the intercalated facial nodes just behind the commissure of the lip along the course of the facial neurovascular bundle.

Nasal Cavity and Paranasal Sinuses. The lymphatics of the nasal cavity are separated into the olfactory group and the respiratory group. According to Rouvière,[13] they do not communicate with each other. There is a connection between the lymphatic network of the olfactory region and the subarachnoid spaces, which allows some absorption of cerebrospinal fluid (CSF) into the lymphatic system. The lymphatics of the olfactory region of the nasal cavity run posteriorly to terminate in lymph nodes alongside the jugular vein at the skull base in the lateral pharyngeal space. The lymphatics of the respiratory nasal cavity terminate in the lateral retropharyngeal nodes or the level II nodes. The capillary lymphatic plexus of the nasal mucosa is probably not very profuse, judged by the relatively low incidence of metastatic nodes.

The mucosa of the paranasal sinuses has either no or very sparse capillary lymphatics.

Pathology

Benign Tumors

Inflammatory polyps, giant cell reparative granulomas, benign odontogenic tumors, and necrotizing sialometaplasia may appear in this area. Inverted papilloma is a benign, aggressive neoplasm that is associated with carcinoma in 5% to 15% of cases.[329]

Malignant Tumors

Nasal Vestibule. Almost all malignant tumors are SCCs; basal cell carcinomas and adnexal carcinomas are also reported.

Nasal Cavity and Paranasal Sinuses. SCC or one of its variants is the most common neoplasm. Minor salivary gland tumors account for about 10% to 15% of neoplasms in this region. Lymphoma and melanoma account for approximately 5% and 1% of cases, respectively. Esthesioneuroblastoma is a neuroendocrine carcinoma that originates from the olfactory mucosa. Sinonasal undifferentiated carcinoma—a more aggressive neuroendocrine malignancy—is sometimes encountered.[330] Soft tissue and bone sarcomas may occur in the nasal cavity and paranasal sinuses, including chondrosarcoma, osteosarcoma, and Ewing sarcoma.[331]

Midline lethal granuloma is a nonkiller (NK) nasal T-cell lymphoma. Unchecked, the disease is fatal. Death results from extension to the CNS, hemorrhage, sepsis, or inanition. Treatment is usually RT, which is often combined with chemotherapy.[332]

Patterns of Spread

Nasal Vestibule

Primary. Lesions of the nasal vestibule invade the alar and septal cartilages and may extend to the nasal skin. The upper lip is frequently invaded. Posterior growth into the nasal cavity is frequent. Early cancers originating on the columella and anterior septum are often superficial lesions that ulcerate and produce a crust or scab and often present with septal perforation.

Lymphatic. Lymph node spread is usually to a solitary ipsilateral level IB node, but may be bilateral. The facial, preauricular, and submental nodes are at small risk. Wallace et al.[333] reported only 4 of 79 patients (5%) with clinically positive lymph nodes at diagnosis, but 9 patients (11%) later developed positive lymph nodes.

Nasal Cavity and Paranasal Sinuses

Nasal Cavity. The routes of spread are essentially the same for various histologies, with the exception of esthesioneuroblastoma and minor salivary gland tumors. The latter have a greater propensity for PNI.

Lesions arising in the olfactory region invade the ethmoids and the orbit, spread through the cribriform plate to the anterior cranial fossa, and spread between bone and dura. Eventually, they penetrate the dura and invade the frontal lobes. These lesions also tend to destroy the septum and may invade through the nasal bone to the skin. Lesions arising on the lateral wall of the nasal cavity invade the maxillary sinus, ethmoids, and orbit.

Esthesioneuroblastomas may show submucosal spread and may grow along olfactory nerves and penetrate through an intact dura to the frontal lobes.

The nasopharynx and sphenoid sinus are secondarily invaded in advanced lesions. The tumor may follow nerves posteriorly and superiorly toward the sphenopalatine ganglion near the skull base or along V2.

Maxillary Sinus. All walls of the sinus may be penetrated by the tumor; the pattern of spread and bone destruction is dependent on the site of origin within the sinus. Lesions arising in the anterolateral infrastructure tend to invade through the lateral inferior wall or grow through dental sockets, causing loosening of the teeth or improper seating of a denture. Ulceration follows, with the development of an oral–antral fistula. Lesions arising on the medial infrastructure readily extend into the nasal cavity.

Posterior infrastructure lesions erode through the posterolateral wall and into the infratemporal fossa and extend superiorly to the skull base. Orbital extension occurs either through the roof of the maxillary sinus, through the ethmoids and lamina papyracea, or by way of the infratemporal fossa and then through the infraorbital fissure.

Tumors arising in the suprastructure of the antrum have two general patterns of development. One group extends laterally, invades the malar bone, and produces a mass below the lateral floor of the orbit that may ulcerate through to the skin. The orbit is invaded laterally and displaces the eye superomedially. The temporal fossa is often involved, as is the zygomatic bone in advanced lesions. Suprastructure cancers that extend medially invade the nasal cavity, the ethmoid and frontal sinuses, the lacrimal apparatus, and the medial inferior orbit.

Ethmoid Sinuses. Depending on the location of the tumor, it may invade the medial orbit through the lamina papyracea, the inner canthus, and the nasal cavity. More advanced lesions invade the maxillary antrum, the nasopharynx, the sphenoid sinus, and the anterior cranial fossa.

Sphenoid Sinus. The sphenoid sinus is closely related to the CNs in the cavernous sinus: III, IV, V1, V2, and VI (Fig. 38.2). CN palsies and headaches are frequently the first clinical evidence of a sphenoid sinus tumor. A diagnosis is usually made, however, when the tumor eventually breaks through into the nasopharynx or nasal cavity where it can be seen.

Inverted Papilloma. A report of 223 cases of inverted papillomas showed the lateral nasal wall was the most commonly involved site (68%), with ethmoid and maxillary sinus involvement also being

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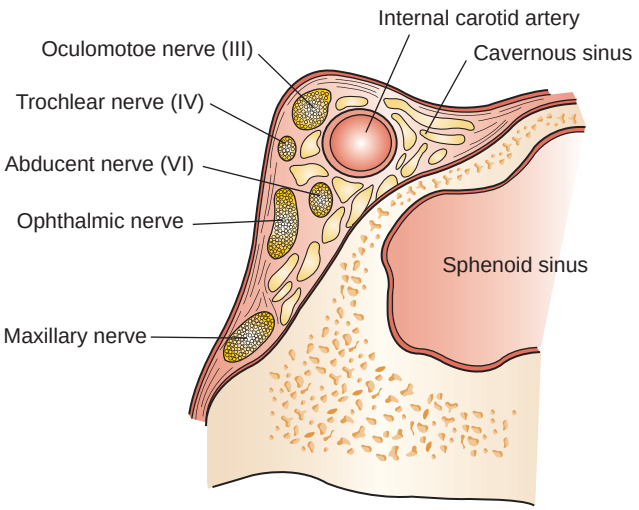

Figure 38.2 Coronal section of the cavernous sinus. (Mendenhall WM, Million RR, Mancuso AA, Stringer SP. Nasopharynx. In: Million RR, Cassisi, eds. *Management of Head and Neck Cancer: A Multidisciplinary Approach,* 2nd ed. Philadelphia: J. B. Lippincott; 1994: 606, Fig. 23-10).

common (57%), as was involvement of the septum (28%). However, ethmoid and maxillary sinus involvement without a tumor of the lateral nasal wall occurred in 4%. Intracranial extension was usually associated with a carcinoma. The tumor occurred bilaterally when there was spread through the nasal septum; multicentric sites of origin were observed.[334]

Lymphatic. The incidence of lymphatic metastases at diagnosis is 10% to 15% for nasal cavity and ethmoid sinus SCCs and probably lower for antral and sphenoid tumors. Maxillary sinus tumors that invade the oral cavity and involve the buccal mucosa, maxillary gingiva, or hard palate may spread to the level IB and level II nodes. Lesions that invade the nasal cavity or nasopharynx spread posteriorly to the parapharyngeal nodes and then to the level II nodes. The risk of cervical node involvement for esthesioneuroblastoma is approximately 20%.[328]

Clinical Picture

Nasal Vestibule

These lesions present with symptoms of a slow-growing mass with attendant crusting and occasional, minor bleeding. Septal perforation may occur.

Nasal Cavity and Paranasal Sinuses

Nasal Cavity. The earliest symptoms are a low-grade chronic infection with discharge, obstruction, and minor, intermittent bleeding. Lesions arising in the olfactory region may cause unilateral or bilateral nasal expansion of the bridge of the nose; a mass may appear near the inner canthus and eventually ulcerate. Obstruction of the nasolacrimal system may be a presenting complaint. Extension through the cribriform plate or into the ethmoid sinuses is accompanied by a frontal headache. The aberration of smell is rare. Invasion of the medial orbit produces proptosis and diplopia; a mass may be palpated in the orbit.

Maxillary Sinus. These cancers develop silently when they are confined to the sinus and produce symptoms after extension through the walls. If the tumor invades toward the oral cavity, the presenting symptoms include pain and loosening or loss of teeth. Palpation and observation of the face may show a mass. A posterior invasion of the orbit will produce proptosis, diplopia, and conjunctival edema. Invasion of V2 in the floor of the orbit may cause paresthesia. Nasal obstruction and bleeding are common, and trismus and headaches are associated with invasion posteriorly into the pterygopalatine fossa, pterygoid muscles, infratemporal fossa, and skull base.

Cancers developing in the medial suprastructure of the antrum present with nasal symptoms of discharge or bleeding, mild infraorbital pain, an infected lacrimal sac, and displacement of the eye superolaterally with proptosis, diplopia, and conjunctival edema.

Cancer developing in the lateral suprastructure produces a mass below the lateral canthus with associated pain. The eye may be deviated medially and upward when orbital invasion occurs, producing diplopia and proptosis. The tumor may extend to the temporal fossa, producing a diffuse fullness.

Ethmoid Sinuses. Mild-to-moderate sinus pain referred to the frontal-nasal area is an early symptom. A painless mass may present near the inner canthus. Diplopia and proptosis develop with invasion of the medial orbit. Nasal discharge, epistaxis, and obstruction are frequent. Paresthesia may occur over the distribution of sensory nerves.

Staging

The AJCC staging system for the nasal cavity and paranasal sinuses is depicted in Table 38.18. Nasal vestibule tumors are staged according to the AJCC staging system for skin cancers.

Treatment

Selection of Treatment Modality

Nasal Vestibule. RT is usually the preferred treatment because of the deformity produced by excision.[333] Surgery alone is preferred for the occasional very small lesion, the removal of which will not produce cosmetic deformity or require reconstruction. A subset of patients best treated by surgery and adjuvant RT or chemoRT are those with invasion of the premaxilla.

Surgical Treatment. Excision of lesions in the nasal vestibule usually involves removal of cartilage as well as skin. Depending on the site of the lesion, the columella, the septum, or the alar cartilages will have to be removed, with a resulting cosmetic deformity that is difficult to reconstruct. If the alar cartilage has been sacrificed, either a composite graft consisting of skin and cartilage from the ear or a nasolabial flap can be used to repair the defect. If the entire external nose is resected, a prosthesis is used.

Irradiation Technique. EBRT, brachytherapy, or a combination of both may be used. EBRT is usually administered with a single anterior portal technique, which uses a combination of photons and electrons; a wax bolus ensures a homogenous dose. The dose ranges from 66 to 70 Gy at 2 Gy per fraction, once daily in a continuous course.

Interstitial brachytherapy of the nasal vestibule and nasal cavity is highly individualized and employs afterloaded ^{192}Ir needles. The implant is usually composed of two, three, or four planes of sources inserted perpendicularly through the skin surface of the external nose with crossing needles placed in the dorsum of the nose, the floor of the nasal cavity, and the upper lip. The dose varies depending on the size of the lesion.[333]

Inverted Papilloma. An inverted papilloma is treated initially by surgery. Depending on the procedure, the local recurrence rate may be fairly high, and subsequent excisions may be required. When the lesion begins to act aggressively with rapid recurrences and invasion of the sinuses, orbit, and anterior cranial fossa, it

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TABLE 38.18

2010 American Joint Committee on Cancer Staging System for Nasal Cavity and Paranasal Sinus Cancers

Maxillary Sinus	
TX	Primary tumor cannot be assessed
T0	No evidence of primary tumor
Tis	Carcinoma in situ
T1	Tumor limited to the maxillary sinus mucosa with no erosion or destruction of bone
T2	Tumor causing bone erosion or destruction including extension into the hard palate and/or middle nasal meatus, except extension to posterior wall of maxillary sinus and pterygoid plates
T3	Tumor invades any of the following: bone of the posterior wall of maxillary sinus, subcutaneous tissues, floor or medial wall of orbit, pterygoid fossa, ethmoid sinuses
T4a	Tumor invades anterior orbital contents, skin of cheek, pterygoid plates, infratemporal fossa, cribriform plate, sphenoid or frontal sinuses
T4b	Tumor invades any of the following: orbital apex, dura, brain, middle cranial fossa, cranial nerves other than maxillary division of trigeminal nerve (V2), nasopharynx, or clivus
Nasal Cavity and Ethmoid Sinus	
TX	Primary tumor cannot be assessed
T0	No evidence of primary tumor
Tis	Carcinoma in situ
T1	Tumor restricted to any one subsite, with or without bony invasion
T2	Tumor invading two subsites in a single region or extending to involve an adjacent region within the nasoethmoid complex, with or without bony invasion
T3	Tumor extends to invade the medial wall or floor of the orbit, maxillary sinus, palate, or cribriform plate
T4a	Tumor invades any of the following: anterior orbital contents, skin of nose or cheek, minimal extension to anterior cranial fossa, pterygoid plates, sphenoid or frontal sinuses
T4b	Tumor invades any of the following: orbital apex, dura, brain, middle cranial fossa, cranial nerves other than V2, nasopharynx, or clivus

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should be considered a low-grade cancer and treated by a more radical removal. RT is recommended for lesions that are incompletely resected, for multiple recurrences, and for those in whom carcinoma is found.[329]

Nasal Cavity. Surgery is the preferred treatment if a gross total resection is likely; postoperative RT or chemoRT is usually indicated.[335] Definitive RT is used for incompletely resectable tumors.

Surgical Treatment. A lateral rhinotomy provides the best access for resection of lesions of the nasal cavity. Generally, reconstruction is not necessary unless the entire cartilaginous septum has been removed, in which case there will be a saddle deformity of the nose. The lateral wall of the nose may be removed by this approach for resection of an inverted papilloma and other localized neoplasms. More advanced lesions require the removal of involved sinuses and orbit. A craniofacial procedure may be required.

Irradiation Technique. The EBRT technique emphasizes an anterior portal with one or two lateral portals. Contiguous structures such as the maxillary sinus, ethmoid sinus, medial orbit, nasopharynx, skull base, and sphenoid sinus are generally included in the initial treatment volume as required. The treatment volume is reduced after 50 Gy to include the original gross disease with a margin. IMRT may be employed and usually produces a more conformal dose distribution.

Advanced lesions may require inclusion of an entire orbit and loss of vision usually occurs, but an operation would require visual loss in any case. Treatment planning should protect the opposite eye and optic nerve.

Combined Treatment Policies

If a combined treatment is planned, we prefer surgery first. RT or chemoRT is started 4 to 6 weeks afterward. The dose is usually 60 to 65 Gy for clear margins; patients with positive margins or for a gross residual tumor after operation receive 74.4 Gy at 1.2 Gy per twice-daily fraction.

Management of Recurrence

Once the patient has had surgery or RT, it is difficult to determine the extent of recurrent disease because of changes from the previous therapy. The most common situation for salvage is RT or surgical failure that can be treated successfully by a craniofacial resection. Tumor extension to the sphenopalatine fossa with definite destruction of a pterygoid plate is a relative contraindication to craniofacial resection. CN involvement, posterior invasion near the optic chiasm, and sphenoid sinus or cavernous sinus invasion are contraindications to resection. An MRI can distinguish between exudate and a gross tumor in a sinus. The anterior wall of the sphenoid sinus may be removed, but the sinus itself cannot be completely resected. Postoperative RT should be considered whether or not margins are positive.

Maxillary Sinus

Selection of Treatment Modality. Surgery gives the best results. Early infrastructure lesions may be cured by surgery alone, but, for most other cases, RT is given postoperatively even if margins are negative. ChemoRT should be considered for a positive margin. The extension of cancer to the skull base, nasopharynx, or sphenoid sinus contraindicates excision. The pterygoid process below the foramen rotundum may be removed along with the attached pterygoid muscles, but destruction of the sphenoid bone above this point is a contraindication to operation. Procedures to resect portions of the skull base are described for special situations.

Surgical Treatment. Surgery for maxillary sinus carcinoma depends on which walls are involved. If the floor of the orbit is free of disease, then the eye and orbital rim may be left undisturbed. If, however, there is involvement through the orbital floor, then a maxillectomy with resection of the floor with or without an orbital exenteration must be performed. If the posterior wall or the pterygoid plates are involved, they too must be included in the resection. A split-thickness skin graft is used to line the cavity, and a removable dental prosthesis is then used to fill the resulting deformity in the palate. An interim prosthesis is constructed prior to surgery so it can be placed at the time of operation and act as a stent. The permanent prosthesis is constructed about 6 months after the operation.

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Irradiation Technique. RT treatment planning includes the entire maxilla, the adjacent nasal cavity, the ethmoid sinus, the nasopharynx, and the pterygopalatine fossa. All or part of the orbit is included in patients with extension into or near the orbit. Target volume definition is aided by the use of treatment planning CT combined with image-fusion MRI. The prescribed dose is 74.4 Gy at 1.2 Gy per fraction twice daily for RT alone. The dose for preoperative RT varies from 50 to 60 Gy, and the dose for postoperative RT varies from 60 to 74.4 Gy.

Ethmoid Sinus

Selection of Treatment Modality. Surgery is preferred if a gross total resection is likely. Postoperative RT or chemoRT is usually indicated. Unresectable tumors are treated with chemoRT.

Surgical Treatment. Localized lesions require resection of the ethmoids with or without the ipsilateral maxilla and/or orbit. Extensive lesions require a craniofacial procedure. Endoscopic resection of selected malignant tumors involving the nasal cavity, ethmoid sinuses, and anterior skull base is being performed with increasing frequency with promising outcomes.

Irradiation Technique. RT treatment is entirely by EBRT, emphasizing treatment through an anterior field combined with one or two lateral fields. This field arrangement, weighted 2:1 or 3:1 in favor of the anterior field, provides adequate treatment of the tumor volume while avoiding excessive RT to the contralateral eye and optic nerve. Wedges are added to achieve a satisfactory dose distribution. Electrons should not be used for the anterior portal. IMRT should be considered because a more conformal dose distribution can usually be achieved.

Management of Recurrence. Recurrent disease is heralded by recurrent pain and CN palsies. Localized recurrence after surgery only may be managed by chemoRT or craniofacial resection and postoperative RT or chemoRT. RT failures may be suitable for maxillectomy or craniofacial resection.

Sphenoid Sinus

The treatment is with RT, and the technique is similar to that used for advanced NPC.

Results of Treatment

Nasal Vestibule

Goepfert and coworkers[336] reviewed the M.D. Anderson Cancer Center experience of 26 patients with nasal vestibule SCCs. The absolute 5-year survival was 78%. Ten patients were treated initially by surgery; one developed a local recurrence and was salvaged by RT. Sixteen patients were treated by RT; three developed local recurrence, and two were salvaged by an operation.

Wallace et al.[333] reviewed 71 patients treated by RT at the University of Florida for SCC of the nasal vestibule. The 5-year local control and cause-specific survival rates were for T1 to T2 (n = 43), 95% and 95%; for T4 (n = 28), 71% and no data; and overall, 86% and 91%.[333] Eight additional patients with unfavorable T4 cancers were treated with resection and adjuvant RT. All eight patients treated with surgery and RT were locally controlled; three of eight experienced severe complications.

Nasal Cavity and Ethmoid Sinus

Inverted Papilloma. Weissler and coworkers[334] reported 233 cases of inverting papilloma seen over a 35-year period. One hundred thirty-four patients had at least 1 year of follow-up. The risk of recurrence was 71% in patients who had an intranasal procedure and 56% for those having a Caldwell-Luc approach. Patients having a lateral rhinotomy had the lowest incidence of recurrence (29%).

Weissler and coworkers[334] also reported six patients who received RT for benign inverting papilloma and nine for inverting papilloma associated with malignant disease. Twelve of the 15 patients had a complete response to RT and were free of disease for long periods of follow-up. Gomez et al.[329] reported 10 patients with advanced and/or recurrent inverting papillomas who were treated with definitive RT. Local recurrence developed in four patients (40%) at 1.5, 6.5, 12, and 13 years after treatment. Six patients remained continuously disease-free at 7, 8.5, 8.5, 9, 9, and 20.5 years after RT.

Carcinoma. Mendenhall et al.[335] reviewed 109 patients treated at the University of Florida for carcinomas of the nasal cavity (69 patients), ethmoid sinus (33 patients), sphenoid sinus (6 patients), and frontal sinus (1 patient). Fifty-six patients were treated with definitive RT, 45 with surgery and postoperative RT, and 8 with preoperative RT and surgery. The 5-year local control rates were for T1 to T3, 82%; for T4, 50%; and overall, 63%. Local control at 5 years was 43% after definitive RT and 84% after surgery and adjuvant RT ($p < 0.0001$). A multivariate analysis revealed that both overall stage and treatment group (definitive RT versus surgery and adjuvant RT) impacted this endpoint. Cause-specific survival rates at 5 years were for stages I to III, 81%; for stage IV, 54%; and overall, 62%. A multivariate analysis of cause-specific survival revealed that T-stage, N-stage, and treatment group significantly impacted this endpoint. Of 109 patients, 31 (20%) sustained severe complications; 17 (16%) of 56 patients after definitive RT, and 14 (25%) of 53 patients after surgery and adjuvant RT.

Esthesioneuroblastoma. Elkon and coworkers[337] reviewed the literature on esthesioneuroblastoma and compiled the results of 78 cases. They concluded that either RT or surgery was sufficient treatment for early-stage disease, but that combined treatment might be advantageous for late-stage presentations. The 5-year absolute survival rate was 75% for lesions confined to the nasal cavity, 60% for those involving the nasal cavity and paranasal sinuses, and 41% for tumors extending beyond the nasal cavity and paranasal sinuses.

Monroe and coworkers[328] reported on 22 patients treated with curative intent at the University of Florida and observed the following 5-year outcomes: local control, 59%; cause-specific survival, 54%; and survival, 48%. The 5-year cause-specific survival rate was lower after definitive RT (17%) compared with craniofacial resection and postoperative RT (56%). Cervical metastases occurred in 6 of 22 patients (27%). Recurrence in the neck was observed in 4 of 9 patients, who were initially N0 and who did not receive elective neck RT compared with zero of 11 patients who were electively treated ($p = 0.02$).

Maxillary Sinus

Waldron and coworkers[338] reported on 110 patients treated with curative intent at the Princess Margaret Hospital with definitive RT (83 patients) or surgery and adjuvant RT (27 patients). The 5-year rates of local control and cause-specific survival were 42% and 43%, respectively. Sixty-three patients developed a local recurrence, and 25 of 63 underwent salvage surgery with a subsequent 5-year cause-specific survival of 31%.

Complications of Treatment

Surgery

Complications of a maxillectomy include failure of the split-thickness skin graft to heal, trismus, CSF leak, and hemorrhage.

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Complications of ethmoid sinus surgery include hemorrhage, meningitis, CSF leak, cellulitis and pansinusitis, brain abscess, and stroke. Complications of craniofacial resection includes meningitis, subdural abscess, CSF leak, diplopia, and hemorrhage.

Radiation Therapy

The most frequent and significant complications of RT involve the eye.[335,339,340] When only a portion of the ipsilateral eye is irradiated (the medial one third), it is possible to preserve vision in the majority of patients. When there is extensive disease in the orbit, however, the entire eye is irradiated to a high dose with almost certain loss of vision; however, these same patients would require orbital exenteration if treated by surgery. The risk for bilateral blindness can be reduced by the use of CT and MRI scans for improved treatment planning and knowledge of the tolerance of the optic nerve.

A few patients will experience a transient CNS syndrome that includes vertigo, headaches, decreased cerebration, and lethargy. This syndrome usually appears 2 to 3 months after the completion of treatment and lasts 1 to 2 months. Aseptic meningitis, chronic sinusitis, or serous otitis media can occur. High-dose RT of the nasal cavity can cause narrowing and synechiae of the nasal cavity. Douching with salt water and daily self-dilations with petrolatum-coated cotton swabs will reduce the problem. Septal perforations occur when tumor has destroyed part of the septum; these do not usually require treatment. Destruction of the nasal bone and septum by the tumor may result in cosmetic deformity. Maxillary necrosis may develop, particularly if teeth are extracted.

PARAGANGLIOMAS

Paragangliomas are an uncommon group of neoplasms that may originate anywhere glomus bodies are found. The lesions are rare before the age of 20; there is a female predominance in some series; and the lesions may occur in multiple sites in about 10% to 20% of cases, especially in patients with familial history. Carotid body tumors are associated with conditions producing chronic hypoxia, such as high-altitude habitation.

Anatomy

The normal glomus bodies in the head and neck vary from 0.1 to 0.5 mm in diameter. Tumors arising in glomus bodies (i.e., paragangliomas) arise most often from the carotid and temporal bone glomus bodies, with rare reports of tumors arising in the orbit, nasopharynx, larynx, nasal cavity, paranasal sinuses, tongue, and jaw. The temporal bone glomus bodies are not found consistently in any location. At least one half of the glomus bodies are found in the general region of the jugular fossa; the remaining are distributed along the course of the nerve of Jacobson (a branch of CN X). Approximately 20% of all temporal bone glomus bodies lie in the tympanic canaliculus, and approximately 10% are in relation to the cochlear promontory. The carotid bodies are located adjacent to the bifurcation of the common carotid. Orbital bodies are in relation to the ciliary nerve, and vagal bodies are adjacent to the ganglion nodosum of the vagus nerve.

Pathology

Paragangliomas are histologically benign tumors resembling the parent tissue and consist of nests of epithelioid cells within stroma-containing, thin-walled blood vessels and nonmyelinated nerve fibers. Although the tumor is well circumscribed, a true capsule is not seen. The criterion of malignancy is based on the development of metastases rather than the histologic appearance.

Patterns of Spread

These lesions usually grow slowly; it is usual to have a history of symptoms for a few years and, occasionally, for 20 years or longer.

Carotid Body Tumors

Carotid body tumors are usually located at the common carotid bifurcation and, as they expand, tend to displace and encircle the internal and external carotid vessels. The tumor begins in the adventitia of the artery and initially derives its blood supply from the vaso vasorum. An accessory blood supply may come from branches of the vertebral artery and the ascending cervical artery. The tumor is usually closely adherent to the wall of the carotid adjacent to the vascular pedicle, and there may be thinning of the arterial wall owing to pressure by the mass. Large masses extend toward the cervical spine, skull base, angle of the mandible, and the lateral pharyngeal space.

Temporal Bone Tumors

Glomus tympanicum lesions tend to be small when diagnosed because they produce symptoms early in their course. The tumor may involve the ossicles, the tympanic membrane, the mastoid, the external auditory canal, the semicircular canal, and the 7th, Jacobson, and Arnold nerves.

Glomus jugulare tumors invade the skull base, petrous apex, jugular vein, middle ear, and middle and posterior cranial fossae. CNs V to XII may be involved.

Lymphatic

Lymphatic metastases occur in about 5% of carotid body tumors but are very rare for temporal bone tumors. An upper neck mass may be an inferior extension of a jugular fossa or vagal tumor rather than a lymph node metastasis.

Distant Metastases

Distant metastases have rarely been reported for temporal bone tumors; carotid body tumors have a low risk for distant metastases, probably in the range of 5% or less.

Clinical Picture

Carotid Body Tumors

The most common presenting symptom is an asymptomatic, slow-growing mass in the upper neck near the carotid bifurcation. Large masses may encroach on the parapharyngeal space and produce dysphagia, pain, and CN palsies. Carotid sinus syndrome may occur because of the pressure of the mass.

On examination, the mass usually lies deep to the sternocleidomastoid muscle and is tethered to surrounding structures. Fixation occurs only in large tumors extending to the spine and skull base. Glomus vagale tumors occur more superiorly and produce a submucosal bulge in the tonsillar area.

Temporal Bone Tumors

A tumor arising in or near the middle ear presents with an insidious conductive hearing loss, pulsatile tinnitus, vertigo, and headache. Patients with lesions developing in or around the jugular fossa develop headaches, often pulsatile in nature, referred to the orbit or temple. CNs V to XII and the sympathetic nerves become affected. Lesions developing in the facial canal present with facial nerve symptoms.

A characteristic blue-red mass may be seen bulging the tympanic membrane. A mass may be appreciated in the upper neck between the mandible and mastoid. Paralysis of CNs V to XII and sympathetic nerves may occur.

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Differential Diagnosis

Carotid Body Tumors

The differential diagnosis includes enlarged lymph nodes, a carotid artery aneurysm, a branchial cleft cyst, benign tumors (e.g., lipoma), and direct extension of a lateral pharyngeal wall or pyriform sinus cancer into the soft tissues of the neck.

A CT and/or MRI scan with contrast provides the diagnosis. A biopsy usually produces serious hemorrhage and is not recommended.

Temporal Bone Tumors

The differential diagnosis includes an internal carotid artery in the middle ear either as an aberrant vessel or as an aneurysm. These patients also present with hearing loss, pulsatile tinnitus, and a pulsatile mass behind the eardrum. A high jugular bulb may present as a vascular mass in the middle ear and mimic a glomus tumor. Other possibilities include an ear canal polyp, an NPC with extension to the temporal bone, acoustic neuroma, middle ear carcinoma, metastatic carcinoma, cholesteatoma, histiocytosis, chronic serous otitis, and mastoiditis.

Staging

There is no accepted staging system for paragangliomas.

Treatment

Selection of Treatment Modality

Temporal Bone Tumors. Excision is satisfactory for small lesions that can be removed without a risk of operative death or damage to normal structures. Stereotactic radiosurgery is an option for early lesions.

Early lesions of the tympanic cavity are managed successfully by excision without a loss of hearing or vestibular function. The remainder of the lesions are managed best by RT, with a very high success rate and minimal morbidity with current techniques. Partial removal of the tumor prior to RT does not improve the results and only increases the overall morbidity. Local control after RT is defined as stable disease or partial regression with no evidence of growth.

Carotid Body Tumors. Small lesions (1 to 5 cm) may be successfully removed with little risk to the patient. However, if resection of the carotid vessels is anticipated or if a large lesion is fixed or unresectable because of size, RT is the preferred initial treatment.

Surgical Treatment

Temporal Bone Tumors. Small glomus tympanicum lesions are approached through the eardrum or mastoid area and are removed. Hearing loss may occur from the operation, but if there is conductive hearing loss from the tumor, it may be correctable.

For the glomus jugulare tumors, surgery is reserved for RT failure, in which case a radical mastoidectomy or a subtotal temporal bone resection would be required. Some surgeons advocate a skull base approach.

Carotid Body Tumors. A standard neck incision is made in a skin crease at the level of the carotid bulb, and the carotid sheath and its contents are identified. The tumor is usually lying at the bifurcation of the internal and external carotid arteries, often displacing these vessels. Marked drops in blood pressure and bradycardia can be avoided by injecting the bulb area with lidocaine. Bleeding may be avoided by using the bipolar electrode before excising the mass. The mass is then removed, preserving the carotid arteries. Preoperative embolization of feeder vessels is frequently employed to minimize intraoperative blood loss.

Irradiation Technique

RT consists of 45 Gy of 25 fractions over 5 weeks. The dose is below the tolerance of the normal tissues included in the treatment volume. Patients are treated with IMRT.

Acute RT sequelae are almost nil. The patient will have temporary hair loss in the entrance and exit areas beginning about the 3rd week. Mild nausea may occur. Late sequelae are few. The patient may develop otitis media, especially if tumor involves the middle ear.

Management of Recurrence

Patients have follow-up with annual CT or MRI scans. Recurrence after surgery usually is treated by RT. Recurrence after RT should be treated by operation if feasible; if surgery is not possible, re-RT may be considered.

Results of Treatment

Woods and coworkers[341] observed a local control rate of 89% in 71 patients with temporal bone paragangliomas who were treated surgically and followed from 1 to 22 years. Green and coworkers[342] reported a local control rate of 89% after surgery for 18 patients who had a mean follow-up of 8 years.

Hinerman et al.[25] reported on 104 patients with 121 paragangliomas who were treated with RT (115 tumors) or radiosurgery (6 tumors) and followed for a median of 8.5 years. The 10-year actuarial local control and cause-specific survival rates were 94% and 95%, respectively.

Complications of Treatment

Surgery

The major risks during operation are hemorrhage and injury to the CNs. Other complications include hemiparesis, spinal fluid leak, and hearing loss.

Irradiation

Complications include cholesteatoma and sequestrum of the mastoid and otitis media. Detectable damage to the hearing mechanism and vestibular apparatus is unlikely after 45 Gy of 25 fractions.[343]

MAJOR SALIVARY GLANDS

Tumors of the major salivary glands account for 3% to 4% of all head and neck neoplasms. The average age of patients is 55 years for malignant neoplasms, and about 40 years for benign tumors. Approximately 25% of parotid tumors and 50% of submandibular tumors are malignant.

Anatomy

The parotid gland is formed by the muscles, bones, vessels, and nerves that come in contact with the gland. The bulk of the parotid gland is superficial, extending superiorly to the zygomatic arch and anterior aspect of the external auditory canal. The anterior border does not extend beyond the opening of the parotid duct into the oral cavity opposite the second molar. Inferiorly, the gland extends between the mastoid and the angle of the mandible. The gland lies in front of and below the external auditory canal. A deep lobe extends into the parapharyngeal area, where it is in

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relationship to the lateral process of C1, the styloid process, and the parapharyngeal space.

The parotid gland is encompassed by fascia that is sufficient to contain most parotid infections in addition to benign tumors and low-grade malignancies. However, the fascia between the parotid gland and the conchal and tragal cartilages is thin and quickly penetrated by tumor. The fascia separating the deep lobe from the parapharyngeal space (stylomandibular fascial membrane) may be sufficiently thin to allow the tumor or infection to access the parapharyngeal space and pharynx.

The sensory nerve supply to the parotid area and part of the pinna is from the greater auricular nerve (C2 to C3). The facial nerve (VII) penetrates the parotid gland almost immediately upon leaving the stylomastoid canal and forms an extensive anatomic network within the gland and gives off branches to the muscles of expression.

The parotid gland is richly supplied from several arteries that freely anastomose and create arteriovenous bleeding during a parotidectomy. The external carotid, the internal maxillary and superficial temporal arteries, and the posterior facial vein lie deep to CN VII.

The superficial preauricular nodes lie outside the fascia of the parotid gland and immediately in front of the tragus and drain the skin of the anterior ear, temple, and upper face, including the eye and nose. They are involved most frequently by metastatic skin cancer and lymphoma, but not usually from parotid neoplasms. The preauricular nodes empty into the external jugular chain nodes, or they may communicate with the internal jugular chain nodes.

There are two nodal groups within the parotid fascia. Within the substance of the parotid gland are numerous lymph follicles and 4 to 10 small lymph nodes scattered along the posterior facial and external jugular veins. Thus, they may lie deep to CN VII. Outside the gland but within the fascia are subparotid nodes that lie in front of the tragus and between the inferior aspect of the parotid tail and the anterior border of the sternocleidomastoid muscle.

Pathology

Benign Tumors

Benign Mixed Tumors. Also called pleomorphic adenoma, these slow-growing neoplasms are surrounded by an imperfect pseudocapsule traversed by fingers of tumor. The age of appearance begins in the early 20s with a mean age of 40 years.

Papillary Cystadenoma Lymphomatosum. Also called a Warthin tumor, it is encased by a thin but complete capsule, occurs predominantly in older men, is bilateral in approximately 10% of cases, and may be multiple on one or both sides.

Benign Lymphoepithelial Lesions. Benign lymphoepithelial lesions account for about 5% of benign lesions. The tumor may be bilateral and is more common in women.

Oncocytoma. Oncocytoma is a benign, slow-growing tumor found mostly in the older age group. The encapsulated tumor has a dark appearance similar to melanoma.

Basal Cell Adenoma. The basal cell adenoma is an uncommon benign lesion, usually appearing in older people. It is cured by a simple excision. Basal cell adenoma must be distinguished from basal cell carcinoma of the skin metastatic to parotid lymph nodes.

Malignant Tumors

Low-Grade Malignancy

Acinic cell carcinoma. Acinic cell carcinomas typically are indolent low-grade neoplasms appearing in all age groups and are most common in women. Metastases occur in a small percentage of cases and cannot be predicted by the histologic picture.

Mucoepidermoid carcinoma, low grade. Most mucoepidermoid carcinomas are indolent lesions readily cured by adequate excision. They may appear in any age group and grow slowly; there is little or no capsule. They are usually well circumscribed, but they may widely infiltrate the normal gland or become fixed to skin.

High-Grade Malignancy

Mucoepidermoid carcinoma, high grade. High-grade mucoepidermoid carcinomas behave aggressively, widely infiltrating the salivary gland and producing lymph node and distant metastases. They may be difficult to distinguish from SCCs.

Adenocarcinoma, poorly differentiated carcinoma, anaplastic carcinoma, and squamous cell carcinoma. These histologies tend to appear late in life and behave aggressively. Almost all of the so-called SCCs of the parotid are metastatic from skin cancer, especially from the temple area.[344]

Malignant mixed tumor. A small percentage of benign mixed tumors may develop into a frank malignancy (carcinoma ex pleomorphic adenoma).

Adenoid cystic carcinoma. This is uncommon in the major salivary glands. Its growth rate is variable. Metastases to regional lymph nodes and distant sites occur; PNI is characteristic; and recurrences may appear many years after initial treatment.

Lymphoepithelioma (malignant lymphoepithelial lesion, "eskimoma"). Lymphoepithelioma occurs rarely in the parotid and submandibular gland. The histologic picture is that of lymphoepithelioma with varying degrees of nonmalignant lymphoid stroma.

Patterns of Spread

Benign Mixed Tumors

Benign mixed tumors of the parotid gland grow by expansion and local infiltration. Most tumors begin in the superficial lobe. Because of their slow growth, they rarely cause CN VII palsy. When incompletely excised, multiple tumor nodules develop within the tumor bed. Skin invasion may occur in recurrent lesions; bone invasion does not occur.

Malignant Tumors

Malignant neoplasms infiltrate the parotid gland, invade CN VII and the auriculotemporal nerve, and spread along nerve sheaths. The tumor may invade the adjacent skin, muscles, and bone. Deep lobe lesions invade the parapharyngeal space, the infratemporal fossa, and the skull base and compromise additional CNs.

Malignant tumors of the submandibular gland invade the gland, fix the tumor to the adjacent mandible, and invade the mylohyoid muscle and hypoglossal nerve.

Sublingual gland neoplasms usually present as a submucosal mass in the floor of the mouth. The advanced lesions show an ulcerated mass in the floor of the mouth with extension to the tongue, the mandible, and the submental soft tissues.

Lymphatic Spread

Lymph node metastases may occur from all of the malignant neoplasms. Approximately 20% to 25% of patients with malignant tumors will have clinically positive or occult metastases in lymph nodes at the time of diagnosis. Low-grade mucoepidermoid carcinoma and acinic cell adenocarcinoma have a low rate of lymph node metastasis, as do adenoid cystic cancers. The risk for lymph

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node metastasis increases with recurrent disease and an increased size of the primary lesion.

Clinical Picture

Parotid Gland

The majority of patients with either benign or malignant parotid tumors present with a mass. Mild, intermittent pain is occasionally present, but does not distinguish between benign and malignant tumors. Facial nerve palsy is an infrequent presenting complaint and indicates malignancy. Deep lobe tumors may produce dysphagia. Fixation or reduced mobility may occur in both benign and malignant neoplasms. Tumors presenting in the deep lobe may cause bulging of the palate and tonsil. Advanced malignant lesions may rarely affect CNs IX to XII and the sympathetic chain if the parapharyngeal space is invaded. CN V3 may be involved when tumor tracks along the auriculotemporal nerve to the skull base; pain is an associated finding.

Submandibular Gland

Both benign and malignant neoplasms present as a mass usually associated with mild pain. Nerve palsy is rarely present. The skin may be infiltrated in advanced lesions. The tumor mass usually is partially fixed to the mandible unless quite small. Loss of mobility occurs with both benign and malignant lesions.

Sublingual Gland

Sublingual gland lesions are clinically similar to floor of the mouth SCCs. They produce a mass, which is submucosal at first, that may be felt by the tongue. There is mild discomfort, if any, in the early stages.

Differential Diagnosis

Parotid Gland

Gallia and Johnson[345] reviewed 140 patients who eventually underwent a parotidectomy for diagnosis. Only 11% had malignant masses; the remainder had benign neoplasms (62%) or nonneoplastic conditions (27%). Conditions that may be confused with a parotid tumor include: (1) metastatic cancer, lymphoma, or leukemia involving parotid-area lymph nodes; (2) fatty replacement, tail of parotid; (3) chronic parotitis; (4) a Boeck sarcoid; (5) a stone in the duct; (6) cysts (branchial cleft, dermoid); (7) hypertrophy associated with diabetes; (8) hypertrophy of masseter muscle; (9) mandibular neoplasms; (10) prominent transverse process of C1; (11) penetrating foreign bodies; (12) hemangiomas/lymphangioma; and (13) a lipoma.

Submandibular Gland

The differential diagnosis of a submandibular mass includes inflammatory disease, SCC metastatic to a lymph node, and a primary neoplasm of the submandibular gland.

Gallia and Johnson[345] reviewed 110 submandibular lesions in patients who underwent biopsy. Ninety-three lesions (85%) were nonneoplastic, usually inflamed glands, and nine lesions (8%) were benign tumors. Eight patients (7%) had malignant lesions, of which three lesions were lymphoma, three were metastatic carcinoma, and two were primary submandibular gland carcinoma.

Biopsy Technique

Parotid Gland. The biopsy and definitive surgical treatment are often the same for parotid masses. Lesions lying in the superficial lobe are best biopsied by performing a superficial parotidectomy. Lesions involving both the superficial and deep lobes or just the deep lobes are "biopsied" by a total parotidectomy. An incisional and excisional biopsy may contaminate the tumor bed, thus increasing the risk of tumor recurrence and facial nerve damage as well as increasing the extent of the definitive surgical procedure by necessitating the wide removal of the biopsy site.

An FNA cytology can be performed for diagnosis. A negative FNA does not necessarily mean that there is no tumor, therefore surgical decisions often rely heavily on clinical and radiographic findings. An FNA can be used in the inoperable or recurrent lesions when RT is the initial treatment.

Submandibular Gland. An FNA is helpful when positive for a tumor, but may delay diagnosis when falsely negative. When needle biopsy is negative, but history, physical examination, and radiographic studies suggest neoplasm, and a careful search of the head and neck area fails to reveal a primary mucosal lesion, the submandibular triangle is dissected as the biopsy procedure.

Staging

The AJCC staging system is depicted in Table 38.19.

Treatment

Selection of Treatment Modality

Parotid Gland. The initial management of resectable superficial lobe parotid masses is an en bloc superficial lobectomy. The tumor usually can be dissected free of the facial nerve. If the tumor involves the deep portion of the gland, the nerve is retracted and the deep portion excised (i.e., total parotidectomy). Skin, bone, and muscle may also be resected as needed.

Low-grade malignant neoplasms are usually managed by operation only. RT is given postoperatively for nearly all high-grade lesions. RT is advised for low-grade malignant lesions that are recurrent and those with close or positive margins on the facial nerve. Postoperative RT is advised for selected benign mixed tumors when there is microscopic residual disease after operation, and for nearly all patients after surgery for recurrent disease. RT alone is unlikely to control gross disease, and if possible, resection of any gross residual benign mixed tumor should be performed prior to RT. Inoperable malignancies are treated by definitive RT.

TABLE 38.19

2010 American Joint Committee on Cancer Staging for Major Salivary Gland Primary Tumors (T)

TX	Primary tumor cannot be assessed
T0	No evidence of primary tumor
T1	Tumor 2 cm or less in greatest dimension without extraparenchymal extension[a]
T2	Tumor more than 2 cm but not more than 4 cm in greatest dimension without extraparenchymal extension[a]
T3	Tumor more than 4 cm and/or tumor having extraparenchymal extension[a]
T4a	Tumor invades skin, mandible, ear canal, and/or facial nerve
T4b	Tumor invades skull base and/or pterygoid plates and/or encases carotid artery

[a] Extraparenchymal extension is clinical or macroscopic evidence of invasion of soft tissues. Microscopic evidence alone does not constitute extraparenchymal extension for classification purposes.

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Submandibular Gland. If a frozen section diagnosis shows a malignant lesion and there is no involvement of nerves, mandible, or soft tissues, submandibular triangle dissection is performed and postoperative RT is given to the submandibular bed and ipsilateral neck. If there is PNI, bone invasion, a clinically positive node, or extension to contiguous soft tissues, resection is enlarged to encompass the necessary areas. Postoperative RT is added in nearly all cases.

Surgical Treatment

Superficial Parotidectomy. The incision is made in the preauricular crease and then curves under the earlobe posteriorly, and extends into the neck. The facial nerve is identified and the dissection is carried out between the mass and the facial nerve. Ideally, a 1-cm circumferential cuff of "normal" parotid tissue should be resected along with the tumor. However, close margins of less than 1 mm are frequently encountered because most parotid gland tumors lay close to branches of the facial nerve. In such cases, completely encapsulated tumors can frequently be resected with confidence. On the other hand, facial nerve sacrifice must be considered if the nerve branch courses directly through the tumor or when there is gross extracapsular extension into the parotid gland. The adequacy of resection is determined by frozen sections.

Total Parotidectomy. A superficial parotidectomy is performed, the nerve is dissected free from the underlying deep lobe, and the deep lobe and tumor are removed. Occasionally, the mandible must be divided to gain access to the retromandibular portion of the deep lobe. A partial mandibulectomy is required when the mandible is invaded by tumor.

The intraparotid nodes are removed with the primary lesion. If the nodes are positive, a neck dissection is added. Neck dissection is always included for clinically positive nodes. Elective neck dissection is not done for low-grade lesions.

A radical parotidectomy implies removal of the entire parotid, the facial nerve, and other involved tissues such as skin, bone, or muscle. Part or all of CN VII must be sacrificed, and an immediate autologous nerve graft may be done. If a frozen section examination of the facial nerve is positive at the stylomastoid foramen, a mastoidectomy may be required to complete the resection. Postoperative RT is delayed for 6 weeks, and the chance of successful function is reported to be good.[346]

Radiation Therapy

The minimum treatment volume for parotid lesions includes the parotid bed and upper neck nodes. PNI indicates enlargement of the portals to cover the nerve pathways. The entire ipsilateral neck is included for high-grade lesions or for clinically positive nodes in the neck dissection specimen. The tumor dose to the primary area is 60 to 65 Gy over 6 to 7 weeks if there is no gross residual disease. Higher doses employing altered fractionation are used for patients with microscopically positive margins or gross disease.

Submandibular space EBRT portals are tailored to the extent of disease found in the surgical dissection. The entire ipsilateral neck is included. The postoperative dose is 65 to 70 Gy because the rate of recurrence, even with combined treatment, is substantial. Neutron therapy has been used in the management of unresectable salivary gland cancers.[347]

Chemotherapy for Salivary Gland Cancers

Historically, chemotherapy has been primarily used for patients with incurable disease or on prospective clinical trials. The safety and dosing of concurrent chemotherapy and RT has been established for this body region from the experience in patients with upper aerodigestive tract SCCs, and as such, this approach is sometimes applied to patients with unresectable disease or in the poor risk adjuvant setting. Available efficacy data for such an approach in this setting are limited.[348,349]

Results of Treatment

Parotid Gland

Benign Mixed Tumors. Enucleation or excision with a narrow rim of normal tissue will eventually result in a local recurrence rate of approximately 20% after 10 to 15 years of follow-up. A superficial parotidectomy will result in a recurrence rate of approximately 5%.[350] The surgical success rate for recurrent lesions depends on the number of previous operations and the size and extent of recurrence. It may be necessary to sacrifice one or several branches of CN VII and to repair the defect with a nerve graft. Postoperative RT of 66 to 70 Gy is added in selected cases in which there are close margins or microscopic residual disease, or in cases in which a subsequent recurrence would be almost impossible to manage surgically or would result in loss of the facial nerve.[351] Death because of benign mixed tumors is unlikely.

Malignant Tumors. The likelihood of cure after surgery alone for low-grade tumors is high, and adjuvant RT is usually unnecessary. The local recurrence rate for operation alone is approximately 50% to 60% for high-grade tumors.[352,353]

Garden and coworkers[354] reported 166 patients treated with surgery and postoperative RT for parotid malignancies at the M.D. Anderson Hospital between 1965 and 1989. Forty patients (24%) developed a recurrent disease that was local in 9% and regional in 6%. The histologic type did not significantly influence the likelihood of local control ($p = 0.36$). Twenty-five patients (15%) developed distant metastases with disease control above the clavicles. The 10- and 15-year survival rates were 60% and 52%, respectively.

Submandibular Gland

Byers and coworkers[355] reported the results of treatment for 22 malignant tumors of the submandibular gland with no prior therapy. Treatment was resection followed selectively by postoperative RT. The local control rate was 64%, and the survival rate was 50%.

Spiro[350] reported the results of surgery for 129 malignant submandibular gland carcinomas seen between 1939 and 1973. All patients had a minimum of 10 years of follow-up. Adenoid cystic carcinoma occurred in 35%, mucoepidermoid carcinoma in 29%, and malignant mixed tumor in 19%. Cervical lymph nodes were malignant in 28%. The local–regional control rate was 40%, and the cause-specific cure rate was 31% at 5 years and 22% at 10 years.

Benign tumors of the submandibular gland were resected in 106 patients, and only 2 developed a local recurrence.[350]

Chemotherapy Results

The heterogeneity and relative rarity of malignant salivary gland tumors have complicated the evaluation of systemic therapies. Prospective clinical trials are infrequent; different histologies are often combined, as are the results for major and minor salivary gland tumors. Over the last 2 decades, less than 500 patients with adenoid cystic cancer have been the subject of studies evaluating drug therapy.[356,357] Drugs like doxorubicin and 5-fluorouracil with reported activity have this claim largely based on retrospective case series, not prospective clinical trials.

Cisplatin, paclitaxel, vinorelbine, epirubicin, and mitoxantrone have major response rates in the 10% to 20% range in prospective studies in the recurrent or metastatic disease setting.[358–362] The potential importance of histology in trial design is well illustrated with the case of paclitaxel, where 3 out of 12 and 4 out of 17 patients with mucoepidermoid and adenocarcinoma responded, respectively, yet zero of 14 with adenoid cystic cancer responded.[363] Treatment with gemcitabine also did not yield any major response

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in patients with adenoid cystic carcinoma.[139] Cisplatin- or anthracycline-containing combinations (e.g., cyclophosphamide/doxorubicin/cisplatin; cisplatin/vinorelbine; cisplatin/5-fluorouracil, cisplatin/mitoxantrone) may increase this rate, but a major response still occurs in the minority of patients, and toxicity is increased.[356,357] The relative efficacies of single-agent versus combination chemotherapies have not been well studied. It should be emphasized that the natural history of some salivary gland cancers, of which the adenoid cystic subtype is perhaps the best example, can be quite indolent, making initial observation a prudent course.

Given these response rates, clinical trials are often an attractive option for patients, and there has been interest in the potential utility of newer targeted agents. Expression of potential molecular targets vary by pathologic subtype. For example, c-kit is commonly expressed in adenoid cystic cancer, but variably or not at all in other salivary cancer subtypes.[356] Although there have been reported responses to imatinib in case reports,[364,365] demonstrating objective responses in clinical trials where the agent has proved elusive, and so the drug remains investigational for this disease.[366,367] Data thus far for EGFR pathway and Her-2 targeted agents are limited and not compelling.[368] Of note, the androgen receptor is commonly expressed in patients with salivary duct carcinoma, and there are reports under these circumstances of response to antiandrogen therapy.[369] The oncogenic transcription factor c-myb is overexpressed in adenoid cystic cancer[370] and is informing further drug development in the disease. Dovitinib, which is designed to block fibroblast growth factor receptor (FGFR)- and vascular endothelial growth factor receptor (VEGFR)-mediated angiogenesis demonstrated activity in a phase II trial in patients with adenoid cystic cancer.[371]

Complications of Treatment

Surgery

Facial paralysis is the most important complication associated with parotid surgery. Temporary facial nerve palsy may occur due to manipulation of the nerve during operation, and function will gradually return over a few months' time. Isolated persistent weakness of the lower lip may occur due to division of the platysma muscle. Incomplete eyelid closure requires protective measures such as artificial tears, Lacri-Lube (Allergan Inc., Irvine, CA), and eye patches to prevent corneal abrasion. A variety of surgical techniques can be employed to address facial nerve deficits if functional recovery is not expected, including nerve grafting, a brow lift, gold weight implantation into the upper eyelid, lower eyelid tightening, and facial suspensory procedures. Gustatory sweating (Frey syndrome) occurs in about 10% of patients after parotidectomy and rarely requires treatment. A persistent salivary fistula is rare.

Radiation Therapy

Xerostomia is avoided by techniques that spare the contralateral salivary tissues. There may be trismus due to fibrosis of the masseter and pterygoid muscles and the temporomandibular joint. Otitis media may occur if the ear is irradiated. Localized hair loss may occur with some techniques. Osteoradionecrosis may rarely occur with high doses.

MINOR SALIVARY GLANDS

Tumors of the minor salivary gland origin are uncommon, accounting for about 2% to 3% of all malignant neoplasms of the upper aerodigestive tract. They may appear at any age, but are uncommon before age 20 and rare under age 10. They tend to occur most often in the hard palate, nasal cavity, and paranasal sinuses—areas infrequently involved by SCCs. Thus, the site of origin is related to the density of the minor salivary glands in a particular tissue.

Anatomy

Minor salivary glands are ubiquitous in the mucosa of the upper aerodigestive tract with the exception of the gingivae and the anterior portion of the hard palate, which are free of minor salivary glands. They are distributed on the undersurface of the anterior and lateral oral tongue and the base of the tongue. Aberrant salivary tissue sometimes is seen in lymph nodes, in the body of the mandible just behind the third molar teeth, and in the vestigial remnant of the nasopalatine canal in the anterior maxilla, middle ear, lower neck, sternoclavicular joint, thyroglossal duct, and other sites.

Pathology

Approximately one half of minor salivary gland tumors are malignant. The histologic varieties of malignant tumors include adenoid cystic carcinoma, mucoepidermoid carcinoma, adenocarcinoma, and malignant mixed, acinic cell, and oncocytic carcinomas. About two thirds are adenoid cystic. Mucoepidermoid carcinomas and adenocarcinomas arise predominantly in the oral cavity.

The benign tumors are pleomorphic adenomas in the great majority of cases, with a few cases of intraductal papillomas, papillary cystadenomas, basal cell adenomas, and benign oncocytomas.

Patterns of Spread

There are no minor salivary glands in the anterior half of the hard palate, so tumors arise on the posterolateral hard palate and all of the soft palate. The site of origin for floor of mouth salivary gland tumors is either the sublingual gland or a minor salivary gland.

These tumors grow by local infiltration with eventual invasion of muscle, bone, and cartilage. PNI is a common feature, particularly for adenoid cystic carcinoma. The tumor may track both centrally and peripherally along nerves, but the central spread is the more common event. Extension along nerves eventually may traverse the skull base and surface intracranially, although this spread pattern may not become manifest for several years after the original treatment. Tumor growth along a nerve may be characterized by skip areas, so that a normal nerve segment is no assurance of free margins.

The risk of positive lymph nodes is related to the site of origin and the histology. Lymph node metastases are most likely from sites with a dense capillary lymphatic network, similar to the pattern for SCC. Adenoid cystic carcinoma, low-grade mucoepidermoid carcinoma, and acinic cell carcinoma are at low risk to spread to lymph nodes; about 20% of adenoid cystic carcinomas spread to lymph nodes, but this low incidence may be related partly to their frequent site of origin in the hard palate and paranasal sinuses, areas that infrequently produce lymph node metastases. The high-grade tumors carcinomas have a 30% incidence of lymph node involvement on presentation, and eventually half will develop lymph node metastases.

Clinical Picture

The clinical picture depends on the site of origin. The signs and symptoms differ from those of SCCs arising in the same area. Many of the lesions are indolent, and the history may go back many months or even years. Because lesions develop under the epithelium, the initial lesion is a submucosal mass that is often painless until ulceration develops. PNI is expressed as pain or paresthesias. Otherwise, the clinical picture resembles that for SCCs for a given size and site. Lymph node metastases occur at predictable sites. The clinically positive nodes are usually small and mobile, but neck dissection on such a patient may show numerous small, clinically undetectable positive nodes. The same staging systems applied to SCCs may be used.

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Treatment

Selection of Treatment Modality

Benign, mixed-grade tumors are managed by operation; postoperative RT sometimes is advised in cases in which margins are close or positive.[372]

The low-grade carcinoma is treated initially by an operation when feasible, but RT is sometimes used as the primary treatment for inaccessible lesions or where the functional loss would be considerable. Postoperative RT is added for close margins or for those lesions that have recurred more than once. If the patient presents after excisional biopsy of a small lesion, RT is an alternative to reexcision, particularly if the procedure would produce significant cosmetic or functional loss.

The treatment of high-grade lesions varies immensely, depending on the site of origin, stage of disease, and willingness of the patient to accept a major cosmetic or functional change subsequent to an operation. Surgery and postoperative RT are preferred; RT alone is used for unresectable cancers. There are data that support the use of neutron therapy.[347]

Surgical Treatment

Benign tumors are removed by a wide local excision that includes a cuff of normal tissue. Small, low-grade lesions with a long history of slow growth may be treated with a wide local excision including a shell of normal tissue. Large, low-grade lesions and high-grade lesions require a more radical resection. When PNI is present, it is not possible to remove all the nerves potentially involved, but the nerves that are involved should be sacrificed wherever it is reasonable to do so. As an alternative, postoperative RT may be used to cover the perineural routes of spread.

Irradiation Technique

The RT techniques and doses are similar to those for SCCs of the same anatomic site and similar tumor size, with the exception that nerve pathways must be covered for adenoid cystic carcinomas. Subclinical PNI for adenoid cystic carcinomas must be considered to be present even if it is not seen on the biopsy or surgical sections.

Results of Treatment

Spiro and coworkers[373] reported the Memorial Sloan-Kettering Cancer Center results for 434 malignant minor salivary gland tumors, of which 90% were treated surgically. The cause-specific 5-, 10-, and 15-year cure rates were 44%, 32%, and 21%, respectively; 51% died of the original cancer. Patients with adenoid cystic carcinoma had the poorest prognosis, with about 20% surviving without recurrence. Those with adenocarcinoma had an intermediate outlook—about 35% surviving without recurrence—and mucoepidermoid carcinomas had the best control rate, with about 70% long-term cures.

Cianchetti et al.[18] reported on 140 patients treated at the University of Florida for minor salivary gland carcinomas between 1966 and 2006. The 10-year local control rate was 66%; a multivariate analysis revealed that treatment group and T-stages significantly influenced this endpoint. Patients treated with RT alone had a lower local control rate compared with those treated with surgery and RT. The 10-year outcomes were for distant metastasis-free survival, 67%; for cause-specific survival, 56%; and for overall survival, 45%.

Benign mixed tumors of minor salivary gland origin have a good prognosis. Spiro[350] reported on 81 benign tumors; 60 occurred on the palate and 13 on the lip or cheek. With a minimum follow-up of 10 years, the local recurrence rate was 6%.

Wallace et al.[374] reported on 25 patients treated with RT alone (2 patients) or combined with surgery (23 patients) for pleomorphic adenoma and followed the patients for a median of 10.5 years. Local control was obtained in 13 of 16 patients (75%) with subclinical disease and 5 of 9 patients (56%) irradiated for gross disease. The 10-year overall local control rate was 76%.

In a small randomized trial of inoperable primary or recurrent salivary gland cancers (both major and minor salivary gland cancers were allowed), neutron therapy ($n = 25$) improved local–regional control significantly ($p = 0.009$) but at the expense of more severe morbidity.[347]

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